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OF ORGANIC CHEMICALS

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NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. Preparations appear in alphabetical order of titles of the synthetic procedures. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 8th and 9th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is adopted. For example, both diethyl ether and ethyl ether are normally used. Since ethyl ether is the established *Chemical Abstracts* name for the 8th Collective Index, it has been used in this volume. The 9th Collective Index name is 1,1'-oxybisethane, which the Editors consider too cumbersome. The prefix *n*-is deleted from *n*-alkanes and *n*-alkyls. All reported dimensions are now expressed in Système International units.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds that are of general interest, as well as procedures that illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should be checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yield should be reported rather than the maximum yield obtainable by an operator who has had considerable experience

with the preparation.¹ For each solid product the melting-point range should be reported, and for each liquid product the boiling-point range and refractive index should be included. In most instances it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, mass, or nuclear magnetic resonance spectra, and criteria of purity such as gas chromatographic data. In the event that any of the reactants are not commercially available at reasonable cost, their preparation should be described in as complete detail and in the same manner as the preparation of the product of major interest. The sources of the reactants should be described in the Notes section, and physical properties such as boiling point, index of refraction, and melting point of the reactants should be included except where standard commercial grades are specified.

Beginning with Volume 49, Methods of Preparation (Sec. 3) and Merits of the Preparation (Sec. 4) have been combined into Discussion (Sec. 3). This section should include descriptions of related and practical methods. Other published methods that have no practical synthetic value do not need to be mentioned. Those features of the procedure that recommend it for publication in *Organic Syntheses* should be cited (synthetic method of considerable scope, specific compound of interest not likely to be made available commercially, method that gives better yield or is less laborious than other methods, etc.). If possible, a brief discussion of the scope and limitations of the procedure as applied to other examples, as well as a comparison of the particular method with the other methods cited, should be included. If necessary to the understanding or use of the method for related syntheses, a brief discussion of the mechanism may be placed in this section. The present emphasis of *Organic Syntheses* is on model procedures rather than on specific compounds (although the latter are still welcomed), and the Discussion should be written to help readers decide on the value of the procedure in their research. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. An accompanying letter setting forth the features of the preparations that are of interest or value is helpful to the Board.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary.

CARL ROBERT NOLLER

November 10, 1900–October 20, 1980

Carl Robert Noller, one of the early members of the Board of *Organic Syntheses* and Editor-in-Chief of Volume 15, died at the age of 79 on October 20, 1980 at the Stanford Hospital after a heart attack followed by open heart surgery.

His close colleagues at Stanford University, Professors William A. Bonner, Richard H. Eastman, and Harry S. Mosher write about him as follows.

“Carl was born November 10, 1900 in St. Louis, Missouri. His father, a wagon maker, and his mother, maiden name Laessig, were of German descent. He grew up in St. Louis and obtained his B.S. and M.S. degrees, 1922 and 1923, at Washington University in St. Louis and his Ph.D. degree, 1926, under professor Roger Adams at the University of Illinois. After being an instructor at Northwestern University in 1926–1927 with Frank Whitmore, he spent two years with Eastman Kodak Company in Rochester; then in 1929 he accepted an appointment as Assistant Professor at Stanford. He was awarded a Guggenheim fellowship for six months’ study in Munich and Zürich in 1933. During the academic year of 1938–1939, he was a Visiting Lecturer at Harvard. . . .”

“Professor Noller was most widely known for his textbooks in organic chemistry. His text for majors, *Chemistry of Organic Compounds*, was first published in 1951, followed by second and third editions in 1957 and 1965. There were also two shorter versions, his *Textbook of Organic Compounds* (also three editions) and *Structure and Properties of Organic Compounds*. Approximately 10,000 Stanford students between 1951 and 1970 were introduced to organic chemistry through his books. His texts were rapidly adopted for the organic chemistry courses in a large number of universities in the United States. These books held their favored position for many years. They were recognized internationally by editions in Spanish (Argentine and Mexican editions), Chinese (Asian edition), Yugoslavian, and German. Noller’s was the first text to embrace modern molecular orbital treatment of

chemical bonding. This had an immediate and worldwide impact on the teaching of organic chemistry. His majors text included a wide range of examples of industrial products and processes. By use of special topics chapters and generous footnotes, this volume was encyclopedic in its scope. Because of these features and the meticulously prepared index, it also served as a major reference work and is still widely used for this purpose. These texts have served his students and colleagues as models of clarity, factual integrity, nomenclature, and style for scientific writing. . . ."

"Professor Noller co-authored over one hundred scientific papers with his students. The subjects of these studies evolved over the years, but the central theme interwoven into his broad-ranging research endeavors was the investigation of natural products of plant origin. This interest began with his Ph.D. thesis problem, which dealt with the proof of structure and synthesis of chaulmoogric acid, a substance isolated from chaulmoogra oil which was being used at that time as a topical treatment for leprosy. Subsequent studies included the first total synthesis of oleic and elaidic acids and the isolation of erucic acid from rapeseed oil. Noller then undertook investigations in the areas of steroidal sapogenins and triterpenes. His final major research effort in the natural product field was the investigation of the toxic, bitter constituent of manroot (*Echinocystis fabracea*), a member of the gourd family that was "mined" by Carl and his students along the banks of San Francisquito Creek. Extracts of this plant reportedly were used by the Californian Indians as fish poisons. The active component proved to be the cucurbitacins, which are both chemically and pharmacologically most interesting. They have highly oxygenated steroid-like structures but lack the angular methyl group at C-10 common to other steroids. His interest in the chemistry of plant products and in gardening led Professor Noller to become an amateur botanist with a broad knowledge of the scientific names of the local flora. Along with this natural product research, he and his students conducted experiments on the nature of the Grignard reagent; the mechanism of the Friedel-Crafts reaction, ozonolysis, and catalytic reduction reactions; basic problems in stereochemistry; the synthesis of pyridine and piperidine derivatives; and the use of zinc alkyls, mercury alkyls, and phosphate esters in organic synthesis. He also published several articles on effective lecture demonstrations, especially in the area of stereochemistry."

In addition to his impact internationally on science and education through his textbooks and research publications, Carl Noller played an important domestic role as an educator and scholar. He is remembered particularly for the very high standards of performance he demanded of himself as well as of his students. His intolerance of unscientific thinking and sloppy work was strongly influential in establishing a no-nonsense attitude of scholarly integrity which prevailed in the Stanford Chemistry Department.

WILLIAM S. JOHNSON

December 1982

PREFACE

This volume contains 30 checked procedures. The vast majority of these deal with new synthetic methods and methodology of a general nature. A broad range of synthetic transformations is covered.

The synthesis of PYRUVOYL CHLORIDE from the corresponding acid not only represents the method of choice for the preparation of this substance, but can be applied to other acids as well. A one-pot procedure for the preparation of ETHYL 2-BUTYRYLACETATE illustrates another general method for the synthesis of β -ketoesters. The synthesis of 4-PENTYLBENZOYL CHLORIDE by direct electrophilic substitution of 4-pentylbenzene with phosgene, derived *in situ* from oxalyl chloride, can likewise be applied to other aromatic substrates.

The synthesis of BENZYL ISOCYANIDE from benzaldehyde via reductive amination with 5-aminotetrazole followed by oxidation of the resultant amine with sodium hypobromite provides a general method for the synthesis of isocyanides. The preparation of BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE makes available an alternative to dimethyl azodicarboxylate that is not only more reactive in Diels-Alder reactions but whose ester groups can be removed under neutral conditions.

A wide variety of substituted γ -butyrolactones can be prepared directly from olefins and aliphatic carboxylic acids by treatment with manganic acetate. This procedure is illustrated in the preparation of γ -(*n*-OCTYL)- γ -BUTYROLACTONE. Methods for the synthesis of chiral molecules are presently the target of intensive investigation. One such general method developed recently is the employment of certain chiral solvents as auxiliary agents in asymmetric synthesis. The preparation of (*S,S*)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE FROM TARTARIC ACID DIETHYL ESTER provides a detailed procedure for the production of this useful chiral media; an example of its utility in the synthesis of (+)-(*R*)-1-PHENYL-1-PENTANOL from benzaldehyde and butyllithium is provided.

In contrast to isocyanates, the isomeric cyanates were unknown until recently. These substances undergo a number of useful transfor-

mations. A simple procedure that can be applied to a number of phenols and some acidic alcohols is illustrated in the preparation of PHENYL CYANATE. A procedure which illustrates a general method for converting norcarane derivatives to *endo,endo*-1,3-bridged bicyclobutanes via a carbenoid insertion is shown in the synthesis of 1,6-DIMETHYLTRICYCLO[4.1.0.0^{2,7}]HEPT-3-ENE.

Thiol esters have recently found broad applications in organic synthesis. Two methods for their preparation from acid chlorides and acids are described in the preparation of 2-METHYLPROPANE-2-THIOL ESTERS OF CYCLOHEXANECARBOXYLIC ACID AND CHOLIC ACID. Conversion of the former thiol ester to the corresponding *O*-*t*-butyl ester illustrates a general method for the preparation of *O*-ESTERS FROM THE CORRESPONDING THIOL ESTERS.

The synthesis of ETHYL α -(BROMOMETHYL)ACRYLATE and METHYL α -(BROMOMETHYL)ACRYLATE makes these valuable intermediates readily available for the synthesis of α -methylene- γ -butyrolactone derivatives and other substances as well. A simple procedure for the preparation of 2-alkyl-2-cyclohexenones by reductive alkylation of *o*-anisic acids is demonstrated in the preparation of 2-HEPTYL-2-CYCLOHEXENONE. A remarkable large-scale preparation of a Dewar benzene derivative is illustrated by the preparation of HEXAMETHYL DEWAR BENZENE from dimethylacetylene.

The synthesis of 2-HYDROXYMETHYL-2-CYCLOPENTENONE from cyclopentenone illustrates a general strategy and method for the synthesis of an effective latent synthon of an α -ketovinyl anion. The synthesis of CYCLODODECYL MERCAPTAN from cyclodecanone provides a method for the preparation of secondary or hindered mercaptans which cannot be prepared by traditional displacement reactions.

Emphasis on the employment of transition metal catalysts to achieve useful synthetic transformations is illustrated by three procedures in this volume. The reaction of allylic alcohols with aryl halides in the presence of a palladium derived catalyst can be used to prepare various β -arylaldehydes. This is illustrated by the preparation of 2-METHYL-3-PHENYLPROPANAL. OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T is a novel and useful procedure for the preparation of vicinal hydroxy arylsulfonamides which in turn can be employed in the synthesis of a host of sub-

stances. A closely related procedure illustrated by the synthesis of ETHYL *threo*-[1-(2-HYDROXY-1,2-DIPHENYLETHYL)]CARBAMATE is also provided.

A practical synthesis of 1,3-OXAZEPINES VIA PHOTOISOMERIZATION OF HETEROAROMATIC *N*-OXIDES is illustrated for 3,1-BENZOXAZEPINE. A hydroboration procedure for the synthesis of PERHYDRO-9b-BORAPHENALENE AND PERHYDRO-9b-PHENALENOL illustrates beautifully the power of this methodology in the construction of polycyclic substances. The conversion of LIMONENE TO *p*-MENTH-8-EN-YL METHYL ETHER demonstrates a regio- and chemoselective method for the PHOTOPROTONATION OF CYCLOALKENES. An efficient method for the conversion of a ketone to an olefin involves REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES. A mild method for the conversion of a ketone into the corresponding trimethylsiloxy enol ether using trimethylsilyl acetate is shown for the synthesis of (*Z*)-3-TRIMETHYLSILOXY-2-PENTENE.

A procedure which illustrates a general method for preparing a wide range of spirocyclohexenones and spirocyclohexadienones is provided for SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE. A detailed procedure for the preparation of *trans*-1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE and its employment as a diene in the Diels-Alder reaction illustrates the high nucleophilicity of this important intermediate. A method for the GENERATION AND REACTIONS OF VINYL LITHIUM REAGENTS from ketones via triisopropylbenzenesulfonylhydrazones is presented. Finally, a neat procedure for the fission of *N*-heterocyclic compounds with thiophosgene and base is illustrated in the preparation of *o*-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE from quinoline.

The Board of Editors welcomes both the submission of preparations for future volumes and suggestions for change that will enhance the usefulness of *Organic Syntheses*. Submitters are kindly asked to examine the instructions on pages v and vi that describe the type of preparations we wish to receive and also the information to be included in each contribution. A style guide for preparing manuscripts is available from the Secretary to the Board, and submitters are requested to follow its instructions.

Professor Jeremiah P. Freeman, current Secretary to the Board, has carried on the voluminous correspondence with the submitters and

clickers behind the scenes and provided valuable guidance to the Editor-in-Chief. The *Chemical Abstracts* names and registry numbers in the appendix following each procedure were found and compiled by Dr. Theodora W. Greene who also helped edit this volume. Finally, I would like to acknowledge my secretary, Mandy Ceccarelli, for her skill and diligence in compiling this volume.

CONTENTS

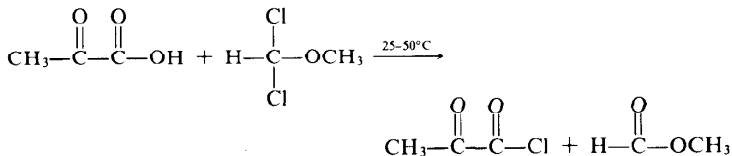
ACID CHLORIDES FROM α -KETO ACIDS WITH α,α -DICHLOROMETHYL METHYL ETHER: PYRUVOYL CHLORIDE	1
ALIPHATIC AND AROMATIC β -KETOESTERS FROM MONOETHYL MALONATE: ETHYL 2-BUTYRYLACETATE	5
PREPARATION OF 4-ALKYL- AND 4-HALOGENOYL CHLORIDES: 4-PENTYLBENZOYL CHLORIDE	8
BENZYL ISOCYANIDE: OXIDATION OF 5-AMINOTETRAZOLES	14
BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE	17
SUBSTITUTED γ -BUTYROLACTONES FROM CARBOXYLIC ACIDS AND OLEFINS: γ -(<i>n</i> -OCTYL)- γ -BUTYROLACTONE	22
CHIRAL MEDIA FOR ASYMMETRIC SOLVENT INDUCTIONS. (<i>S,S</i>)-(+)-1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE FROM (<i>R,R</i>)-(+)-TARTARIC ACID DIETHYL ESTER	24
CYANIC ACID ESTERS FROM PHENOLS: PHENYL CYANATE	35
1,6-DIMETHYLTRICYCLO[4.1.0. ^{2,7}]HEPT-3-ENE	39
ENANTIOSELECTIVE ADDITION OF BUTYLLITHIUM IN THE PRESENCE OF THE CHIRAL COSOLVENT DDB. (+)-(<i>R</i>)-1-PHENYL-1-PENTANOL	42
PREPARATION OF <i>O</i> -ESTERS FROM THE CORRESPONDING THIOL ESTERS	48
ETHYL α -(BROMOMETHYL)ACRYLATE	56
2-HEPTYL-2-CYCLOHEXENONE: ALKYLATION OF THE ANION FROM BIRCH REDUCTION OF <i>o</i> -ANISIC ACID	59
HEXAMETHYL DEWAR BENZENE	62
2-HYDROXYMETHYL-2-CYCLOPENTENONE	65
<i>o</i> -ISOTHIOCYANATO-(<i>E</i>)-CINNAMALDEHYDE	71
MERCAPTANS FROM THIOKETALS: CYCLODODECYL MERCAPTAN	74
METHYL α -(BROMOMETHYL)ACRYLATE	77
2-METHYL-3-PHENYLPROPANAL	82
OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T: <i>cis</i> -2-(<i>p</i> -TOLUENESULFONAMIDO)CYCLOHEXANOL AND 2-METHYL-3-(<i>p</i> -TOLUENESULFONAMIDO)-2-PENTANOL	85
OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY <i>N</i> -CHLORO- <i>N</i> -ARGENTOCARBAMATES: ETHYL <i>threo</i> -[1-(2-HYDROXY-1,2-DIPHENYLETHYL)]CARBAMATE	93
1,3-OXAZEPINES VIA PHOTOISOMERIZATION OF HETEROAROMATIC <i>N</i> -OXIDES: 3,1-BENZOXAZEPINE	98
PERHYDRO-9b-BORAPHENALENE AND PERHYDRO-9b-PHENALENOL	103
PHOTOPROTONATION OF CYCLOALKENES: LIMONENE TO <i>p</i> -MENTH-8-EN-1-YL METHYL ETHER	112
REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES: PREPARATION OF 17 β - <i>tert</i> -BUTOXY-5 α -ANDROST-2-ENE	116

SILYLATION OF KETONES WITH ETHYL TRIMETHYLSILYLACETATE: (<i>Z</i>)-3- TRIMETHYLSILOXY-2-PENTENE	122
SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE	129
PREPARATION OF THIOL ESTERS: THE 2-METHYLPROPANE-2-THIOL ESTERS OF CYCLOHEXANE CARBOXYLIC ACID AND CHOLIC ACID	134
GENERATION AND REACTIONS OF VINYL LITHIUM REAGENTS: SYNTHESIS OF 2-BUTYLBORNENE	141
PREPARATION AND DIELS-ALDER REACTION OF A HIGHLY NUCLEOPHILIC DIENE: <i>trans</i> -1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE	147
CUMULATIVE AUTHOR INDEX FOR VOLUMES 60 AND 61	153
CUMULATIVE SUBJECT INDEX FOR VOLUMES 60 AND 61	155

UNCHECKED PROCEDURES

ORGANIC SYNTHESSES

**ACID CHLORIDES FROM α -KETO ACIDS WITH
 α,α -DICHLOROMETHYL METHYL ETHER:
 PYRUVOYL CHLORIDE
 (Propanoyl chloride, 2-oxo-)**



Submitted by HARRY C. J. OTTENHEIJM and MARIANNE W. TIJHUIS¹

Checked by LARRY A. LAST and ROBERT M. COATES

1. Procedure

A 100-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and a 1.2- by 24-cm vacuum-jacketed Vigreux column which is connected to a condenser, vacuum-takeoff adapter, and fraction collector with three receiving flasks (Note 1). The vacuum-takeoff adapter is attached to a calcium chloride drying tube which is connected to a water aspirator, and the flask is charged with 35.2 g (28.6 mL, 0.40 mol) of pyruvic acid (Note 2). The pyruvic acid is stirred at room temperature as 46.4 g (36.1 mL, 0.40 mol) of α,α -dichloromethyl methyl ether (Note 3) is added slowly over 30 min. Evolution of hydrogen chloride begins after a few minutes. When the addition is complete, the dropping funnel is removed and replaced by a glass stopper. The solution is stirred and heated at 50°C in an oil bath for 30 min (Note 4) while a few drops of methyl formate are collected as the first fraction (Note 5). The condenser is then cooled to -30°C (Note 6) and the receiving flasks are cooled to -50°C with chilled acetone. The aspirator is turned on and the pressure is adjusted to 190 mm. With the oil bath at 50°C, a second fraction, bp 25-35°C (190 mm), is collected. As soon as the head temperature begins to drop, the pressure is reduced to 120 mm and the temperature of the oil bath is raised slowly to 75°C. A third fraction, bp 35-40°C (120 mm), consisting mainly of pyruvoyl chloride is collected (Notes 7 and 8). The second and third

fractions are combined to give 33–41 g of a mixture of pyruvoyl chloride and methyl formate which is redistilled through a 1.4 by 18 cm vacuum-jacketed Vigreux column (Note 1). The condenser and the receiving flasks are cooled to -5°C with chilled acetone. The first fraction, weighing 2.3–11.4 g and consisting mainly of methyl formate, is collected at $25\text{--}30^{\circ}\text{C}$ (190 mm) with an oil bath temperature of 60°C . When the pressure is reduced to 120 mm and the oil bath is maintained at 60°C , 18.6–21.2 g (44–50%) of pyruvoyl chloride, bp $43\text{--}45^{\circ}\text{C}$ (120 mm), distills into the receiver as a light yellow liquid, n_{D}^{20} 1.4165 (Notes 9 and 10).

2. Notes

1. The glassware was dried for 16 hr in an oven at ca. 125°C and assembled while still warm. The checkers used a 27-cm Vigreux column insulated with glass wool instead of the vacuum-jacketed column.

2. Pyruvic acid, supplied by Aldrich Chemical Company, Inc., was freshly distilled: bp $59\text{--}62^{\circ}\text{C}$ (14 mm).

3. α,α -Dichloromethyl methyl ether was purchased from Aldrich Chemical Company, Inc., and redistilled prior to use: bp $83\text{--}84^{\circ}\text{C}$. The reagent may also be prepared from methyl formate and phosphorus pentachloride.² Unlike chloromethyl methyl ether and bis(chloromethyl) ether, α,α dichloromethyl methyl ether is reported to have no significant carcinogenic activity.³ However, as a precaution, the compound should be handled with care in a well-ventilated hood.

4. At this temperature the intermediate, chloromethoxymethyl pyruvate, decomposes to pyruvoyl chloride and methyl formate.⁴

5. The submitters made no effort to collect methyl formate quantitatively. The checkers did not observe the formation of any condensate at this point.

6. This was accomplished by the checkers by passing acetone chilled with dry ice slowly through the condenser jacket. The coolant was contained in a 1-L separatory funnel which was connected to the condenser inlet with a section of Tygon tubing. The effluent was collected in a beaker and periodically returned to the separatory funnel reservoir.

7. Fractions 2 and 3 weighed 10.1–13.4 and 23.6–30.0 g, respectively. Proton NMR spectra of fraction 2 indicated a composition of 70–84% of methyl formate, 16–20% of pyruvoyl chloride, and 0–10%

of unreacted starting materials. The composition of fraction 3 was 21–28% of methyl formate, 60–70% of pyruvoyl chloride, and 1–20% of starting materials. The two fractions collected by the checkers boiled at 25–26°C (190 mm) and 40–46°C (120 mm).

8. For some reactions, such as simple esterification, it is not necessary to distill the acid chloride. The crude reaction mixture may be used provided the hydrogen chloride present is neutralized with an appropriate base.⁵

9. The submitters found that pyruvoyl chloride may be stored at –20°C in carbon tetrachloride solution or as the pure liquid in a sealed tube.

10. The product obtained by the checkers boiled at 48–51°C (120 mm) and was contaminated with ca. 5–10% of methyl formate and unreacted starting materials. The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 2900 (w), 1770 (s, broad), 1415 (m), 1355 (s), 1195 (s), 1130 (m), 1095 (m), 1005 (s), 875 (s); ^1H NMR (CDCl_3) δ : 2.51 (s, 3 H). The compound may be characterized as the *p*-nitroanilide derivative.⁶

3. Discussion

Most of the conventional reagents for the synthesis of acid chlorides from carboxylic acids are unsatisfactory for the preparation of α -keto acid chlorides. For example, the reaction of pyruvic acid with phosphorus halides does not give pyruvoyl chloride⁷ whereas the use of phosgene⁸ or oxalyl chloride^{9,10} affords ether solutions of the acid chloride in low yield. Recently a useful preparation of pyruvoyl chloride from trimethylsilyl pyruvate and oxalyl chloride has been described.¹¹

The use of α,α -dichloromethyl alkyl ethers for the conversion of carboxylic acids to acid chlorides was first reported by Heslinga et al. in 1957.⁴ The submitters have found that the readily available α,α -dichloromethyl methyl ether² is the reagent of choice for the preparation of pyruvoyl chloride.⁶ This simple and economical procedure has been used in other laboratories,^{5,12,13} and the submitters have applied the method to the preparation of three other α -keto acid chlorides: 2-oxobutanoyl chloride (32%), 3-methyl-2-oxobutanoyl chloride (10%), and phenylglyoxylyl chloride (78%).⁶

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Numbers)

Pyruvic acid (8); Propanoic acid, 2-oxo- (9); (127-17-3)
 α,α -Dichloromethyl methyl ether: Ether, dichloromethyl methyl (8);
 Methane, dichloromethoxy- (9); (4885-02-3)
 Methyl formate: Formic acid, methyl ester (8,9); (107-31-3)
 Pyruvyl chloride (8); Propanoyl chloride, 2-oxo- (9); (5704-66-5)

**ALIPHATIC AND AROMATIC β -KETOESTERS
FROM MONOETHYL MALONATE:
ETHYL 2-BUTYRYLACETATE
(Pentanoic acid, 4-methyl-3-oxo-, ethyl ester)**



Submitted by W. WIERENGA and H. I. SKULNICK¹
Checked by STEFAN BLARER, DANIEL WASMUTH, and DIETER SEEBACH

1. Procedure

Ethyl 2-butyrylacetate. In a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, dry nitrogen inlet, and thermometer is placed 19.8 g (0.150 mol) of monoethyl malonate (Note 1), 350 mL of dry tetrahydrofuran (THF, Note 2), and 5 mg of 2,2'-bipyridyl. The solution is cooled to approximately -70°C (in an isopropyl alcohol-dry ice bath) and a 1.6 M solution of *n*-butyllithium in hexane is added from a dropping funnel while the temperature is allowed to rise to approximately -10°C . Sufficient *n*-butyllithium is added (approx. 190 mL) until a pink color persists for several minutes (Note 3). The heterogeneous solution is recooled to -65°C and 7.90 mL (7.98 g, 75 mmol) of isobutyryl chloride (Note 4) is added dropwise over 5 min. The reaction solution is stirred for another 5 min (Note 5) and then poured into a separatory funnel containing 500 mL of ether and 300 mL of cold, 1 *N* hydrochloric acid (Note 6). The funnel is shaken, the layers are separated, and the organic phase is washed with two 150-mL portions of saturated aqueous sodium bicarbonate, followed by 150 mL of water, and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure leaves 11.70 g (98%) of ethyl 2-butyrylacetate (Note 7). The crude product can be distilled at $70\text{--}74^\circ\text{C}$ (7 mm) (80% yield, 96% purity by GLC).

2. Notes

1. The potassium salt of monoethyl malonate, available from the Aldrich Chemical Company, Inc., can be used after neutralization. Direct

use of the potassium salt with only 1 equiv. of *n*-butyllithium gave substantially lower yields. Alternatively, monoethyl malonate can be conveniently prepared in high yield from diethyl malonate.²

2. For smaller-scale reactions, THF was dried and used directly by distillation from sodium/benzophenone, or first from KOH and then from LiAlH₄. The checkers used only dry THF for the present, large-scale procedure as well.

3. Initially, *n*-butyllithium can be added rapidly (20 mL/min) while the cooling bath is removed. A slightly exothermic reaction is noted. Toward the end of the reaction, dropwise addition should be used; the pink color will form and then dissipate. The checkers found it more convenient to use the calculated amount of a freshly titrated³ solution of *n*-butyllithium.

4. Isobutyryl chloride was used as purchased from Aldrich Chemical Company, Inc., or Fluka AG.

5. Reaction times and temperatures vary, depending on the substrate acid chloride (see Table I).

6. For acid chlorides that contain a basic nitrogen, the aqueous phase is adjusted to approximately pH 7 by limiting the concentration of the hydrochloric acid.

7. Gas chromatographic analysis using a 3-ft, 3% OV-17 column at 90°C indicated a purity of 92% (retention time was 3.2 min) with GC-mass spectrometric identification showing M⁺ *m/e* 158 (27%) and the base peak (100%) at *m/e* 113 (C₆H₉O₂). The ¹H NMR spectrum of undistilled material indicates impurities with resonances in the aliphatic region (δ : 1.5–1.0). The checkers recommend distillation of the crude product.

3. Discussion

Since the β -ketoester group is often a key moiety in organic syntheses, a general and efficient route to these 1,3-dicarbonyl compounds is highly desirable. We feel that the one-pot preparation from monoethyl malonate described here⁴ represents an attractive alternative to previous methods⁵ because of the following characteristics: (1) the reaction is general, as demonstrated by the diversity of examples in Table I; (2) the starting materials, (monoethyl malonate and the acid chlorides) are readily available and inexpensive; (3) the yields are high and therefore omission of

purification is possible in many instances; and finally (4) the reaction is simple and easy to scale up.

The optimum ratio for high yields of β -ketoester is 1.7 (monoethyl malonate : acid chloride). A nonstoichiometric reaction for optimum yield is not a serious drawback in this case since the reagent in excess is the inexpensive dilithio monoethyl malonate. Our results show that lowering the ratio also lowers the yield, whereas an increase in the ratio beyond 1.7 has little effect.

TABLE I
REACTION OF ACID CHLORIDES WITH DILITHIO MONOETHYL MALONATE
 $\text{RCOCl} + \text{RCOCH}_2\text{CO}_2\text{C}_2\text{H}_5$

R	Reaction Time (min)/ Temperature ($^{\circ}\text{C}$)	Yield (%) ^a
$\text{CH}_3\text{CH}_2\text{CH}_2$	5/ - 65	95
PhCH_2	5/ - 65	99
Ph	30/ - 65	97
4- $\text{CH}_3\text{OC}_6\text{H}_4$	60/ - 65	90
4- ClC_6H_4	30/ - 65	96
2- ClC_6H_4	30/ - 65	95
2- C_{10}H_7	30/ - 65	95
3-Furyl	15/ - 65, 60 to 0	97
2-Pyrazinyl	15/ - 65, 60 to 0	91

^aThe purity of all products isolated is higher than 90% as determined by GLC or ^1H NMR. The only contaminants appear to be hydrocarbons including *n*-octane.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 2-butyrylacetate: Pentanoic acid, 4-methyl-3-oxo-, ethyl ester (9); (7152-15-0)

Monoethyl malonate: Malonic acid, monoethyl ester (8); Propanedioic acid, monoethyl ester (9); (1071-46-1)

2,2'-Bipyridyl: Bipyridine; 2,2'-Bipyridine (8); 2,2'-Bipyridine (9); (366-18-7)

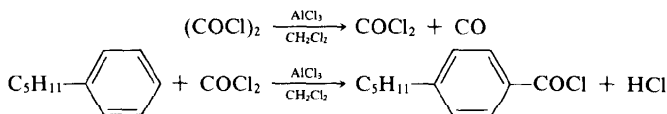
n-Butyllithium: Lithium, butyl (8,9); (109-72-8)

Isobutyryl chloride (8); Propanoyl chloride, 2-methyl (9); (79-30-1)

Potassium monoethylmalonate: Malonic acid, monoethyl ester, potassium salt (8); Propanedioic acid, monoethyl ester, potassium salt (9); (6148-64-7)

PREPARATION OF 4-ALKYL- AND 4-HALOBENZOYL CHLORIDES: 4-PENTYLBENZOYL CHLORIDE

(Benzoyl chloride, 4-pentyl-)



Submitted by MARY E. NEUBERT and D. L. FISHER.¹

Checked by VINAY CHOWDHRY and R. E. BENSON

1. Procedure

Caution! Operations prior to vacuum distillation of the product should be done in a good hood since phosgene, carbon monoxide, and hydrogen

chloride are present (Note 1). Rubber gloves should also be used to avoid contact with the reagents.

A 100-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, 100-mL pressure-equalized addition funnel (Note 2) to which is attached a drying tube (Note 3), and a rubber septum. Dry methylene chloride (27 mL, Note 4) and 8.9 g (0.067 mol) of aluminum chloride (Note 5) are added to the flask, stirring is begun, and 17.1 g (11.5 mL, 0.135 mol) of oxalyl chloride (Note 6) is added over 5 min by means of a syringe introduced through the septum (Note 7). The septum is replaced by a thermometer and a solution of 10 g (11.6 mL, 0.067 mol) of amylbenzene (Note 8) in 40 mL of dry methylene chloride is added dropwise over 1 hr with stirring while the temperature is maintained at 20–25°C. The reaction mixture is reduced to about half of the original volume by distillation of solvent and excess oxalyl chloride and/or phosgene (Note 9). Approximately 40 mL of fresh dry methylene chloride is added to the flask and the solution is cooled to 0°C in an ice-salt bath. The cold solution is slowly poured onto a stirred mixture of 170 g of crushed ice and 10 g of calcium chloride at a rate to maintain the temperature below 5°C (Note 10). The organic layer is rapidly separated from the aqueous layer and dried over anhydrous sodium sulfate. The mixture is filtered and the solvent is removed by distillation at reduced pressure. The residual liquid is dissolved in 50 mL of ether, and the resulting solution is cooled to 0°C, extracted with 5 mL of cold (0°C) 5% potassium hydroxide solution, and then washed twice with 15-mL portions of cold (0°C) water (Note 11). The ether solution is separated and dried over anhydrous sodium sulfate. The mixture is filtered and the solvent is removed by distillation at reduced pressure (Note 12). Distillation through a Vigreux column affords a small forerun and then 7.80–7.82 g (55%) of pure 4-pentylbenzoyl chloride, bp 95°C (0.20 mm) (Notes 13, 14). The acid chloride is stable if kept in a sealed container to prevent hydrolysis.

2. Notes

1. Both phosgene and carbon monoxide were identified in IR spectra of gases generated from an equimolar mixture of oxalyl chloride and aluminum chloride at room temperature.

2. The submitters used a constant addition funnel.

3. Molecular sieves 4A available from Davison Chemical Co. were used.

4. The submitters state that the use of predried methylene chloride (stored overnight over 4A molecular sieves) gave the best results.

5. Use of either an excess of aluminum chloride or partially hydrolyzed aluminum chloride gives larger amounts of the by-product diaryl ketone at the expense of the acid chloride. The checkers used freshly opened containers of the anhydrous material available from Fisher Scientific.

6. Oxalyl chloride should be distilled if it is colored or contains solid. Studies by the submitters have shown that an excess of oxalyl chloride is needed for maximum conversion of the alkylbenzene to acid chloride. The checkers used oxalyl chloride available from Eastman Organic Chemicals.

7. The submitters added the oxalyl chloride through the funnel used to add amylbenzene.

8. The checkers used product available from Aldrich Chemical Company, Inc.

9. If excess oxalyl chloride (and/or phosgene) is not removed, the vigorous reaction with water during decomposition of the aluminum chloride complex contributes to hydrolysis of the product acid chloride by increasing the time needed to complete this step. The more dilute solution achieved by additional solvent helps to prevent this hydrolysis as does maintenance of a low temperature during decomposition of the complex.

10. The calcium chloride-ice mixture helps to maintain a low temperature.

11. Changing the solvent to ether prior to the base extraction step (to remove carboxylic acid formed by hydrolysis) inhibits emulsion formation, particularly with the higher aliphatic-substituted products.

12. The procedure may be interrupted at this point if the crude acid chloride is protected from moisture, although highest yields are obtained if distillation is done at once. Failure to remove water (even that associated with the sodium sulfate drying agent) before storage may result in anhydride formation during distillation because of the presence of free carboxylic acid.

13. Infrared analysis (neat, film) shows a carbonyl doublet at 1740, 1770 cm^{-1} , typical of 4-substituted benzoyl chlorides and thought to be due to Fermi resonance.^{2,3} Contamination of the product with the anhydride can be detected by a doublet at 1720 and 1780 cm^{-1} , with the ketone by a singlet at 1650 cm^{-1} , and with the acid by a singlet at 1690 cm^{-1} .

14. The submitters obtained the product in 75% yield.

3. Discussion

This method is based on that of Fahim,⁴ who isolated 4-alkylbenzoic acids in 40–60% yields by hydrolysis of the corresponding acid chlorides. The present improved procedure includes those conditions believed to be optimum for a one-step synthesis of 4-substituted benzoyl chlorides in good yields and apparently free of positional isomers, as indicated by gas chromatography/mass spectroscopy as well as ¹H and ¹³C NMR analyses. The procedure has been used successfully for the synthesis of 4-halobenzoyl chlorides and several other aryl acid chlorides,^{5,6} as well as for 4-alkylbenzoyl chlorides up through the decyl derivative. Some of these results are summarized in Table I. The reaction has been run on a 1-mol scale by the submitters with no difficulty.

The major by-product that can be isolated (3–6%) from the residue after distillation is the 4,4'-disubstituted benzophenone; formation of the ketone is minimized by using excess oxalyl chloride and by slow addition of a dilute solution of the alkylbenzene to the acylating agent. Ambient temperatures (20–25°C) appear to give optimum results; higher temperatures favor ketone formation and lower temperatures result in incomplete reaction reasonable reaction times. This method cannot be used to prepare acid chlorides of aromatic systems which contain substituents strongly activating for electrophilic substitution such as alkoxy groups (major product is ketone), deactivating ring substituents (no reaction), or those

TABLE I
4-SUBSTITUTED BENZOYL CHLORIDES FROM
SUBSTITUTED BENZENES

Substituent	Yield (%)	bp (°C) (mm)
C ₄ H ₉	66.5	113 (1.7)
<i>i</i> -C ₄ H ₉	77.5	115 (1.6)
C ₆ H ₁₁	75.3	136 (3.2)
C ₆ H ₁₃	80.3	143 (1.3)
C ₇ H ₁₅	79.3	160 (5)
C ₉ H ₁₉	71.8	182 (2.6)
C ₁₀ H ₂₁	68.0	169 (0.6)
F	84.4	50 (1.1)
Cl	77.7	86 (2.1)
Br	75.9	103 (2.5)
I	74.1	100 (0.7)

that form stable acylium ions (major product is carboxylic acid). Mesitoic acid rather than the acid chloride was isolated from the acylation of mesitylene using these conditions, which confirms the results previously reported using similar conditions.⁷

Previously, the most widely used method for preparation of 4-alkylbenzoyl chlorides on a laboratory scale has been from the benzoic acids obtained by oxidation of aromatic ketones, usually 4-alkylacetophenones.⁸⁻¹⁴ The latter are usually prepared by acylating alkylbenzenes. Although this sequence gives high yields, it is lengthy (three completely separate steps) and the scale is restricted in the second step because of the large volumes required. The submitters state that they were unable to repeat the reported alkylation of toluic acid.¹⁵ Methods that lead to formation of ortho and para isomeric intermediates are inconvenient since they require that the isomers be separated.¹⁶⁻¹⁹

This method provides easy access to 4-alkylbenzoyl chlorides, which are useful intermediates in the preparation of diaryl esters that have mesomorphic properties.²⁰ Benzoyl chlorides substituted in the 4-position also serve as starting materials for the preparation of aromatic aldehydes²¹ and nitriles,^{6,22} whereas the acids, derivable quantitatively from the acid chlorides, are good precursors via the Schmidt reaction to 4-substituted anilines.²³

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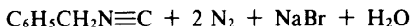
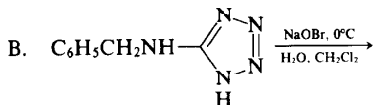
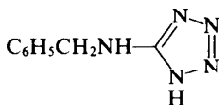
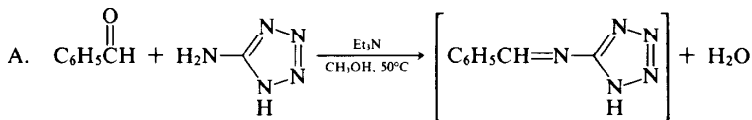
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)
Aluminum chloride (8, 9); (7446-70-0)
Benzene, pentyl (8, 9); (538-68-1)
Benzoyl chloride, 4-pentyl- (9); (49763-65-7)

BENZYL ISOCYANIDE: OXIDATION OF 5-AMINOTETRAZOLES

(Benzene, isocyanomethyl)



Submitted by GERHARD HÖFLE and BERND LANGE¹
Checked by ORVILLE L. CHAPMAN and THOMAS C. HESS

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the obnoxious odor of the isocyanide.

A. *5-Benzylamino-1-tetrazole*. Freshly distilled benzaldehyde (21.2 g, 0.2 mol) is added in one portion to a warm (50°C) solution of 5-aminotetrazole (17.2 g, 0.2 mol) (Note 1) and triethylamine (20.2 g, 0.2 mol) in 100 mL of absolute methanol. After 15 min the reaction mixture is cooled to room temperature, transferred to an autoclave, and hydrogenated with agitation at room temperature over Pd (10%) on carbon (1 g) for 18 hr at 500 psi of hydrogen. The catalyst is removed by filtration and all volatile material is removed at 60°C under aspirator pressure. The gummy tan solid is triturated with 250 mL of hot water. Aqueous 20% HCl is added until pH 3 is reached. The mixture is cooled to room temperature and the solid collected, washed with water, and dried over-

night at room temperature under reduced pressure (100 μ); yield: 27.5 g (80%), mp 183.5–185°C (lit.² mp 183°C).

B. Benzyl isocyanide. In a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing funnel are placed 5-benzylaminotetrazole (10.5 g, 60 mmol), 100 mL of 10% sodium hydroxide solution, and 70 mL of dichloromethane. The mixture is cooled to 0°C and a solution of NaOBr in water (165 mL, 65 mmol) (Note 2) is added with vigorous stirring over a 15-min period (Note 3). The dichloromethane layer is separated and the aqueous phase extracted with five 50-mL portions of dichloromethane. The combined dichloromethane extracts are dried over anhydrous MgSO_4 , the drying agent is removed by filtration, and the dichloromethane is removed by simple distillation. The pressure is then reduced to ~ 20 mm with an aspirator and benzyl isocyanide is distilled at 98–100°C; yield: 5.91 g (84%) (Notes 4 and 5).

2. Notes

1. 5-Aminotetrazole monohydrate is available from Aldrich Chemical Company, Inc.; it was dehydrated by heating over P_2O_5 at 100°C under reduced pressure (100 μ) for 4 hr.

2. The NaOBr solution was prepared according to a procedure described in *Organic Syntheses*.³ Bromine [12.6 g (4 mL, 79 mmol)] was added dropwise with vigorous stirring to 150 mL of a 10% NaOH solution at -10°C . Enough 10% NaOH solution was added to the yellow solution to give 200 mL of reagent.

3. During addition of the NaOBr solution the mixture warms to 20°C. The reaction is virtually instantaneous and can be monitored by the liberated nitrogen.

4. The product was pure by IR and NMR spectroscopy. The IR spectrum showed a very strong band at 2150 cm^{-1} , the NMR spectrum a broad singlet at δ 7.3 (5 H) and a distorted triplet at δ 4.5 (2 H).

5. Glassware can be freed from the odor of isocyanide by rinsing with a 1 : 10 mixture of concentrated hydrochloric acid and methanol.

3. Discussion

By this method high yields of isocyanides are obtained by an oxidation process. Since this oxidation can also be performed anodically or with

TABLE I
PREPARATION OF ISOCYANIDES ($R-N=C$) BY OXIDATION OF 5-AMINOTETRAZOLES

R	NaOBr ^a	Yield (%)		Anodic Oxidation ^a
		Pb(OAc) ₄ /NEt ₃ ^b	Br ₂ /NEt ₃ ^b	
C ₆ H ₅	92	70	43	39
C ₄ H ₉	75			
C ₆ H ₅ CH ₂	84			48

^aIn 2 N sodium hydroxide solution.

^bIn dichloromethane.

bromine or lead tetraacetate and triethylamine in the absence of water (see Table I),⁴ it represents a valuable alternative to other procedures: dehydration reactions,⁵⁻⁷ the alkylation of silver cyanide^{8,9} or the carbylamine (isocyanide) reaction.¹⁰ The starting materials, 5-aminotetrazoles, can be readily obtained by reductive alkylation of 5-aminotetrazole² or from monosubstituted thioureas and sodium azide.¹¹ A limitation of the reaction is that the substituent R must be stable toward oxidation. From a mechanistic point of view the oxidation of 5-aminotetrazoles is a two-step process with a pentaazafulvene as an unstable, undetectable intermediate.

Benzyl isocyanide is a useful precursor of compounds containing the α -benzylamino moiety. Substituted styrenes, vinyl isocyanides, 2-oxazolines, 1-pyrrolines, imidazoles, and α -amino acids and ketones can be obtained by metalation of isocyanides with butyllithium¹² or copper salts,¹³ and subsequent reaction with various electrophiles.¹²

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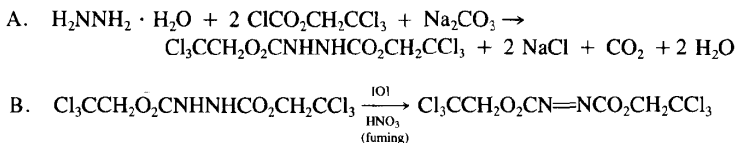
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Benzyl isocyanide (8); Benzene, (isocyanomethyl)- (9); (10340-91-7)
 5-Benzylaminotetrazole: 1*H*-Tetrazole, 5-(benzylamino)- (8); 1*H*-Tetrazol-5-amine, *N*-(phenylmethyl)- (9); (14832-58-7)
 5-Aminotetrazole: 1*H*-Tetrazole, 5-amino-(8); 1*H*-Tetrazol-5-amine (9); (4418-61-5)
 5-Aminotetrazole monohydrate: 1*H*-Tetrazole, 5-amino-, monohydrate (8,9); (15454-54-3)

BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE [Diazenedicarboxylic acid, bis(2,2,2-trichloroethyl) ester]



Submitted by R. DANIEL LITTLE and MANUEL G. VENEGAS^{1,2}
 Checked by SANDY BANKS and ORVILLE L. CHAPMAN

1. Procedure

A. *Bis*(2,2,2-trichloroethyl) hydrazodicarboxylate. In a 500-mL, three-necked flask equipped with mechanical stirrer, thermometer, and 250-mL and 125-mL dropping funnels (Note 1) is placed a solution of 13.34 g (0.23 mol) of 64% hydrazine hydrate (Note 2) in 60 mL of 95% ethanol. The reaction flask is cooled in an ice bath and 96 g (0.46 mol) of 2,2,2-trichloroethyl chloroformate (Note 3) is added dropwise so that

the temperature is kept below 20°C. During the addition of 1 equiv of the chloroformate, a white precipitate is formed. After exactly one-half of the chloroformate has been added, a solution of 25 g (0.24 mol) of sodium carbonate in 100 mL of water is added dropwise along with the remaining chloroformate. The rate of addition of these two reagents is such that the flow of the chloroformate is faster than that of the sodium carbonate so that there is always an excess of chloroformate present; the temperature is kept below 20°C during the addition. As the second equivalent of chloroformate is added the white precipitate dissolves.

After the addition of the reactants is complete, the reaction is allowed to stir for an additional 30 min while the solution warms to room temperature. The reaction mixture is then transferred to a separatory funnel. The viscous organic bottom layer is separated from the aqueous layer and is dissolved in 200 mL of ether. The reaction vessel is washed with 100 mL of ether, and this ether portion is used to extract further the aqueous layer. The ether layers are combined, dried over magnesium sulfate, and filtered, and the solvent is removed under reduced pressure. The viscous oil is allowed to crystallize in an ice bath (0°C). The crystals are collected on a Büchner funnel, washed with 500 mL of water, and dried in a vacuum desiccator at 0.5 mm for 48 hr. 80.8 g (93%) of white crystalline bis(2,2,2-trichloroethyl) hydrazodicarboxylate (mp 85–89°C) is obtained. This material is sufficiently pure for the next preparation. However, further purification can be achieved using an Abderhalden drying apparatus (refluxing 95% EtOH for 12 hr at 0.05 mm; MgSO₄ desiccant). Material purified in this way melted at 96.5–97.5°C (Notes 4 and 5).

B. Bis(2,2,2-trichloroethyl)azodicarboxylate *Caution! Large amounts of nitrogen oxides are evolved during the oxidation with fuming nitric acid. Therefore, operations should be conducted in an efficient fume hood.*

In a 500-mL, three-necked flask equipped with mechanical stirrer, thermometer, pressure-equalizing dropping funnel, and gas outlet tube is added 78.55 g (0.21 mol) of bis(2,2,2-trichloroethyl) hydrazodicarboxylate dissolved in 180 mL of chloroform (Note 6). The solution is cooled to 0°C and 53.2 mL (1.26 mol) of fuming nitric acid (Notes 7 and 8) is added so that the temperature of the solution does not rise above 5°C. The reaction mixture is then allowed to warm slowly to room temperature over 4 hr (Note 9). After an additional 2 hr at room temperature, the material is transferred to and shaken in a 1-L separatory funnel half filled

with ice chips. The two layers are allowed to separate and the bottom organic layer is removed. The aqueous layer is extracted with 250 mL of chloroform. The organic layers are combined and washed with 300 mL of water, 300 mL of aqueous 5% sodium bicarbonate, and again with 300 mL of water. The organic layer is dried with magnesium sulfate, filtered, and the solvent is removed under reduced pressure. The yellow crystals that form are collected on a Büchner funnel and washed with pentane. The pentane filtrate is concentrated under reduced pressure to afford more crystalline material which is again collected on a Büchner funnel and washed with more pentane. The cycle is repeated until no more crystals appear after removal of pentane. The yellow crystals so obtained are air dried for 1 hr to afford 59.2 g (75.8%) of bis(2,2,2-trichloroethyl) azodicarboxylate which melts at 108–110°C. Further drying using an Abderhalden drying apparatus (refluxing 95% EtOH for 12 hr at 0.5 mm; MgSO₄ desiccant) affords a compound that melts at 109–110.5°C (Notes 10 and 11).

2. Notes

1. The thermometer is fitted into one of the necks of the flask so that when it is immersed in the solution, the range between 10 and 20°C is easily visible. A two-necked adapter is used for the dropping funnels.

2. Hydrazine hydrate, 64%, practical grade, was obtained from Matheson, Coleman, and Bell.

3. 2,2,2-Trichloroethyl chloroformate (96%) is commercially available from Aldrich Chemical Company, Inc., and is used without further purification.

4. The average yield obtained for five runs performed by three different people was 83%.

5. The spectral properties of bis(2,2,2-trichloroethyl) hydrazodicarboxylate are as follows: ¹H NMR (CDCl₃) δ: 4.80 (s, 4 H, CH₂CCl₃), 7.0–7.6 (s, br, 2 H, –NH, the position is concentration dependent).

6. The solution can be warmed gently without harm to facilitate solution of the hydrazo compound.

7. Mallinckrodt fuming nitric acid (90–95%, *d* 1.5) was used.

8. The reaction seems to be surprisingly dependent on the amount of nitric acid used. A run with 78.6 g of hydrazo compound and a sixfold excess of nitric acid was quenched after 22 hr and afforded 100% conversion to the desired azo compound (NMR analysis). Another run with

80.0 g of hydrazo compound and a fivefold excess of nitric acid gave only 92% conversion after 25 hr. In another run with 2.0 g of hydrazo compound and a sixfold excess of nitric acid the reaction was complete after 4 hr. In addition, the oxidation was found to be temperature dependent. For example, in a run in which the temperature was maintained between 0 and 5°C for 3 hr and the solution was not allowed to warm to room temperature, only 18% yield was obtained (NMR analysis).

9. The evolution of large amounts of nitrogen oxides was noticed after approximately 1.5 hr (the temperature had reached 13°C).

10. Yields ranged from 76 to 94% (six runs performed by three different people).

11. The NMR spectrum (CDCl_3) for bis(2,2,2-trichloroethyl) azodicarboxylate shows only a singlet at δ 5.05.

3. Discussion

Bis(2,2,2-trichloroethyl) azodicarboxylate has been prepared by oxidation of bis(2,2,2-trichloroethyl) hydrazodicarboxylate with dinitrogen tetroxide.³

Bis(2,2,2-trichloroethyl) azodicarboxylate is a yellow crystalline material which is stable indefinitely in a vacuum desiccator stored in the dark. This compound offers a number of important advantages over diethyl and dimethyl azodicarboxylate for the synthesis of azo compounds. Probably the most important advantage is that in contrast to the ethyl and methyl esters, the trichloroethyl ester grouping can be removed under neutral conditions—a requirement when the product of the transformation is acid or base labile.⁴ Furthermore, in contrast to dimethyl azodicarboxylate and diethyl azodicarboxylate, which have been known to explode when heated and which require distillation for purification, bis(2,2,2-trichloroethyl) azodicarboxylate is isolated as a crystalline solid requiring no heating whatsoever. Another advantage is that Diels-Alder cycloadducts with bis(2,2,2-trichloroethyl) azodicarboxylate are often crystalline solids which can be purified by recrystallization. This is in marked contrast to the viscous oils that are often obtained when the commercially available diethyl azodicarboxylate is used. Finally, we have found that Diels-Alder cycloadditions using bis(2,2,2-trichloroethyl) azodicarboxylate often proceed faster and at a lower temperature than that required for the dimethyl and diethyl analogues (e.g., reaction with 6,6-dimethylfulvene and 6-acetoxyfulvene).

1. Department of Chemistry, University of California, Santa Barbara, CA 93106.
2. The authors wish to thank Ahmed Bukhari for the data which he supplied for this publication.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Numbers)

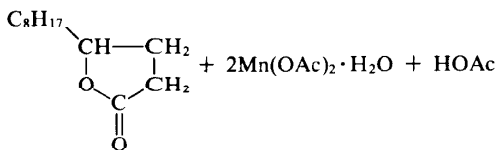
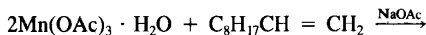
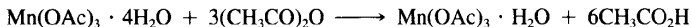
Bis(2,2,2-trichloroethyl) azodicarboxylate: Diazenedicarboxylic acid, bis(2,2,2-trichloroethyl) ester (9); (38857-88-4)

Hydrazine hydrate: Hydrazine monohydrate (8, 9); (7803-57-8)

2,2,2-Trichloroethyl chloroformate: Formic acid, chloro-, 2,2,2-trichloroethyl ester (8); Carbonochloridic acid, 2,2,2-trichloroethyl ester (9); (17341-93-4)

Bis(2,2,2-trichloroethyl) hydrazodicarboxylate: 1,2-Hydrazinedicarboxylic acid, bis(2,2,2-trichloroethyl) ester (9); (38858-02-5)

**SUBSTITUTED γ -BUTYROLACTONES
FROM CARBOXYLIC ACIDS AND OLEFINS:
 γ -(*n*-OCTYL)- γ -BUTYROLACTONE
(2(3*H*)-Furanone, dihydro-5-octyl-)**



Submitted by E. I. HEIBA, R. M. DESSAU, A. L. WILLIAMS and P. G. RODEWALD¹
Checked by GERALD E. LEPONE and ORVILLE L. CHAPMAN

1. Procedure

A 1-L, four-necked flask is fitted with a nitrogen inlet tube, stirrer, dropping funnel, and thermometer. Acetic acid (558 g) is introduced and 107.6 g (0.439 mol) of manganese acetate tetrahydrate (Note 1) is added with stirring and heating under nitrogen. When the temperature reaches 90°C, 16.5 g of solid potassium permanganate (0.104 mol) is added. After the temperature has again fallen to 90°C, 175 mL (189 g, 1.86 mol) of acetic anhydride (Note 2) is added. When the temperature rise has ceased, 44.0 g of 1-decene (0.312 mol) (Note 3) is introduced, followed at once by 250 g of anhydrous sodium acetate. The reaction mixture is then heated to reflux (134°C pot temperature). After 2 hr of reflux under nitrogen the reaction mixture, now clear yellow, is diluted with 1-L of water. The crude product is extracted into 200 mL of benzene, and the aqueous layer again washed with 100 mL of benzene. Benzene is distilled from the combined extracts to give 55.1 g of lactone and 1-decene. 1-Decene is removed by vacuum distillation, followed by the lactone, which distills at 98–99°C (0.05 mm) (Note 4). The yield of γ -(*n*-octyl)- γ -butyrolactone is 34.1 g (66% based on potassium perman-

ganate. However, the lactone yield based on olefin consumed is greater than 95%.)

2. Notes

1. The checkers used manganous acetate tetrahydrate obtained from Fisher Scientific Company. This compound is more readily available than manganous acetate dihydrate used by the submitters and obtained from the Harshaw Chemical Company.

2. If the dihydrate is used, only 76.7 g (0.751 mol) of acetic anhydride is required.

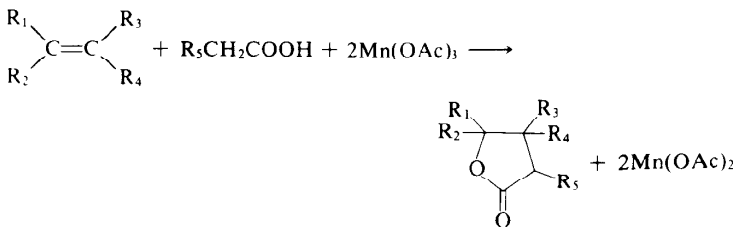
3. 1-Decene was used as obtained from the Humphrey Chemical Company.

4. The checkers found the yield based upon olefin consumed to be 85%. This discrepancy could be accounted for by losses due to the high volatility of 1-decene at reduced pressure.

3. Discussion

This method has the advantage that it does not require the preparation and purification of solid manganic acetate dihydrate. Dehydration by various ratios of acetic anhydride to manganese shows that in this procedure the yield (35%) from the monohydrate is greater than that from the manganic acetate dihydrate. Further removal of all water from the manganic acetate by means of acetic anhydride does not improve the yield (66%).

This general procedure can be used to prepare a wide variety of substituted γ -butyrolactones which depend on the structure of the olefin and the aliphatic acid used. The free radical mechanism and scope of this reaction are described in detail in a paper by Heiba, Dessau, and Rodewald.²



1. Mobil Research and Development Corporation, Central Research Division, P.O. Box 1025, Princeton, NJ 08540.
2. Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7877-7981.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

γ -(*n*-Octyl)- γ -butyrolactone: 2(3*H*)-Furanone, dihydro-5-octyl- (8, 9); (2305-05-7)

Acetic acid (8, 9); (64-19-7)

Manganese acetate tetrahydrate: Acetic acid, manganese(2+) salt, tetrahydrate (8, 9); (6156-78-1)

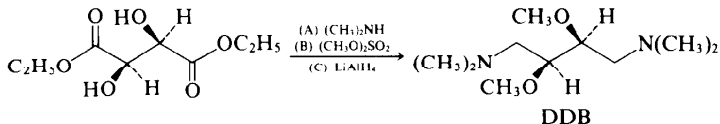
Potassium permanganate; (7722-64-7)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

1-Decene (8, 9); (872-05-9)

CHIRAL MEDIA FOR ASYMMETRIC SOLVENT INDUCTIONS. (*S,S*)-(+)-1,4-BIS(DIMETHYLAMINO)- 2,3-DIMETHOXYBUTANE FROM (*R,R*)- (+)-TARTARIC ACID DIETHYL ESTER

(1,4-Butanediamine, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[*S,S*]-)



Submitted by DIETER SEEBACH, HANS-OTTO KALINOWSKI, WERNER LANGER, GERHARD CRASS, and EVA-MARIA WILKA¹

Checked by M. F. SEMMELHACK and DIANE FACCILOLO

1. Procedure

A. (*R,R*)-(+)-*N,N,N',N'*-Tetramethyltartaric acid diamide. Into a mixture of 618 g (3 mol) of diethyl tartrate (Note 1) and 600 mL of freshly distilled methanol in a 2-L Erlenmeyer flask is poured at least

450 mL (7 mol) of liquid, anhydrous, cold (-78°C) dimethylamine (Note 2). The mixture is swirled briefly, and then allowed to stand in a hood for 3 days with a drying tube in place. After seeding (Note 3) and cooling in a refrigerator overnight, the massive crystals are collected by suction filtration. The filtrate is concentrated, seeded, and cooled to yield a second crop. The combined crystals are washed with cold methanol (-30°C) and dried under reduced pressure at 70 – 100°C (oil bath). The diamide thus obtained is sufficiently pure to be used in the following step. The yield is 570 – 580 g (93 – 95%). Recrystallization from methanol/ethyl acetate furnishes an analytically pure sample, mp 189 – 190°C , $[\alpha]_{\text{D}} +43^{\circ}$ (ethanol, c 3.0)

B. *(R,R)-(+) -2,3-Dimethoxy-N,N,N',N'-tetramethylsuccinic acid diamide.* Into a 4-L, three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and stopper, are introduced 240 mL of 50% aqueous sodium hydroxide (3 mol), 1.5 L of methylene chloride, 0.2 g of benzyltriethylammonium chloride (TEBA), and then 260 g (2.06 mol) of dimethyl sulfate (Note 4). The mixture is stirred vigorously (Note 5), and a total of 204 g (1 mol) of the powdered tartaric acid diamide is added in portions at such a rate as to maintain refluxing (Note 6). Stirring is continued for 24 hr without heating, whereupon 1 L of water is added. Separation of the organic phase, extraction of the aqueous layer with three 300-mL portions of methylene chloride, drying of the combined organic solutions over sodium sulfate, and removal of the solvent in a rotary evaporator (bath temperature below 80°C , water aspirator vacuum) furnishes a slightly yellow oil which crystallizes at 25°C and is sufficiently pure for use in the following reduction step. Recrystallization from cyclohexane/benzene yields 220 g (95% , Note 7) of colorless prisms, mp 63.2 – 63.5°C , $[\alpha]_{\text{D}} +116^{\circ}$ (benzene, c 3).

C. *(S,S)-(+) -1,4-Bis(dimethylamino)-2,3-dimethoxybutane (DDB).* A 4-L, three-necked, round-bottomed flask is fitted with a heating jacket, mechanical stirrer, reflux condenser with drying tube, and a stoppered, pressure-equalizing dropping funnel, flushed with nitrogen or argon, and charged with 2.2 L of dry tetrahydrofuran (THF, Note 8) and 60 g (1.6 mol) of lithium aluminum hydride (LiAlH_4 , Note 9). A mixture of 250 mL of THF and 232 g (1.0 mol) of the diamide is added, with stirring, at a rate sufficient to reach and maintain refluxing. After the addition is completed, the reaction mixture is kept boiling for 2 hr. The flask is immersed in an ice bath, and 60 mL of water, 180 mL of 10% aqueous potassium hydroxide, and again 60 mL of water are added cautiously with very vigorous stirring. The hydrogen gas that is generated is led

well above the stirring motor into the hood exhaust. Temporarily, the slurry becomes viscous and difficult to stir; during this period addition has to be made extremely carefully. The pale yellow, completely hydrolyzed slurry is filtered by suction, the filter cake extracted twice by refluxing with THF in a round-bottomed flask, and the combined solutions are concentrated in a rotary evaporator. The residual liquid is distilled through a 20-cm Vigreux column; bp 62–64°C (3 mm), yield 180 g (88%). For use in organometallic reactions, DDB is freshly distilled from LiAlH_4 . $[\alpha]_{\text{D}} +14.7^\circ$ (neat), d_4^{20} 0.896 (Note 10).

2. Notes

1. Commercial (*R,R*)-(+)-diethyl tartrate can be used. The submitters prepared it from (*R,R*)-(+)-tartaric acid (Firma Renckiser, D-Indwigshafen or Firma Boehringer, D-Ingelheim), $[\alpha]_{\text{D}} +12.7^\circ$ (water, *c* 17): a 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, water separator for organic solvents heavier than water, and a stopper is charged with 1.5 kg (10 mol) of tartaric acid, 1.5 L (26 mol) of 96% ethanol, 1 L of chloroform, and 30 g of freshly activated (1 *N* HCl), highly acidic ion exchange resin (Lewatit 3333). The stirred mixture is heated at reflux until no more water separates (up to 60 hr). Filtration, evaporation, and vacuum distillation (oil bath temperature must not exceed 145°C, no column, fast distillation) yield 1.85 kg (90%) of the ester, $[\alpha]_{\text{D}} +8.16^\circ$ (neat).

2. Dimethylamine (bp 6°C) is condensed into a 1-L flask cooled to –78°C and fitted with an inlet tube and an opening protected from atmospheric moisture with a silica gel drying tube. It is either taken from a cylinder or freed from 1.5 L of a stirred 40% aqueous solution by heating at 60–80°C with 50 g of potassium hydroxide and leading the amine vapors first through a reflux condenser, then through a 50-cm (2 cm I.D.) drying tube filled with potassium hydroxide pellets, and finally into the receiver flask cooled to –78°C.

3. Sometimes spontaneous crystallization occurs; if it does not, a small amount of the solution is withdrawn and evaporated on a watch glass, and the crystals that are obtained by scratching with a glass rod are used for seeding.

4. Dimethyl sulfate was purchased from Riedel de Haen, D-Seelze-Hannover, and used without purification. Because of its high toxicity and carcinogenicity, it should be handled only in a well-ventilated hood.

5. Since the reaction mixture becomes very gelatinous upon addition of the tartaric acid amide, a powerful motor and a large stirring blade are necessary.

6. Since dimethyl sulfate decomposes rapidly in concentrated alkaline medium, addition of the powdered tartaric acid amide must begin *immediately* after the dimethyl sulfate is introduced. The amide should be added *as fast as possible* (ca. 20–30 min) within the limits of the capacity of the reflux condenser and the mechanical stirrer. The amount of dimethyl sulfate can be increased up to 2.5 equivalents and fresh benzyltriethylammonium chloride can be added toward the end of the addition. With less rapid addition and stirring, the yield drops to 45–55%.

7. The yield obtained by the checkers was 78%.

8. Tetrahydrofuran (THF) was obtained from BASF AG, D-Ludwigshafen, and was distilled twice from potassium hydroxide pellets.

9. Lithium aluminum hydride (LiAlH_4) was used as a white powder purchased from the Metallgesellschaft AG, D-Frankfurt.

10. The specific rotation is highly sensitive to the water content of the DDB; only material distilled from LiAlH_4 shows this value.

3. Discussion

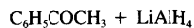
The three compounds whose syntheses are described in the present procedure have been reported previously by the submitters.^{2,3}

The amino ether DDB has been used extensively as a chiral solvent for asymmetric syntheses.²⁻⁸ It is readily available on a large scale in both enantiomeric forms: starting from the unnatural (*S,S*)-(–)-tartaric acid,⁹ (–)-DDB is equally accessible³ following the procedures described herein.

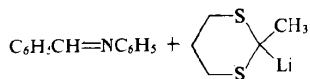
As demonstrated by the examples listed in Table I, DDB induces chirality in enantioface, enantiotope, and enantiomer differentiating¹⁰ reactions in which it acts as a metal (Li, Mg, Cu, Zn) complexing ligand, as a hydrogen-bond mediating component, and as a base catalyst. It can be used at temperatures as low as -150°C if mixed with appropriate cosolvents.³ It is readily recovered and separated from products by acid extraction during work-up. The enantiomeric excess (e.e.) obtained in this asymmetric induction is generally in the range of 10–20%; in optimized and/or fortuitous cases, optical yields of up to 50% have been obtained. The chemical yields are as high as in conventional achiral solvent systems. An application of DDB is described in the following *Organic Syntheses* procedure.

TABLE I
ASYMMETRIC SYNTHESSES WITH (+)-DDB AS A CHIRAL AUXILIARY AGENT¹⁻⁸

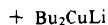
Reagents	Conditions (DDE : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, c) (%, c.c)
$C_6H_5CHO + Bu_2Mg$	2 : 1, -78, ether	$C_6H_5\overset{\overset{OH}{ }}{CH}C_4H_9$	-2.5° (C ₆ H ₆ , 7.0) (8)
$C_6H_5CHO + BuLi$	10 : 1, -150, pentane	$C_6H_5\overset{\overset{OH}{ }}{CH}C_4H_9$	+7° (neat) (40)
$C_6H_5CHO + i\text{-}PrLi$	4 : 1, -120, pentane	$C_6H_5\overset{\overset{OH}{ }}{CH}\text{-}i\text{-}Pr$	+6.1° (ether, 7.5) (14)
$C_6H_5CHO + (C_6H_5S)_3CLi$	10 : 1, -78, pentane	$C_6H_5\overset{\overset{OH}{ }}{CH}C(SC_6H_5)_3$	+23° (C ₆ H ₆ , 1.03) (12)
$C_6H_5CHO - CH_3\overset{\overset{NO}{ }}{N}CH_2Li$	10 : 1, -78, pentane	$C_6H_5\overset{\overset{OH}{ }}{CH}CH_2\overset{\overset{NO}{ }}{N}CH_3$	+6.5 (CH ₂ Cl ₂ , 3.0) (14.8)
$C_6H_5CHO + CH_2=\overset{\overset{OLi}{ }}{C}-O\text{-}t\text{-}Bu$	10 : 1, -78, pentane	$C_6H_5\overset{\overset{OH}{ }}{CH}CH_2\overset{\overset{O}{ }}{C}-O\text{-}t\text{-}Bu$	+5.1° (C ₆ H ₆ , 11.1)
$C_6H_5CHO + CH_2=\overset{\overset{OLi}{ }}{C}NMe_2$	10 : 1, -78, pentane	$C_6H_5\overset{\overset{OH}{ }}{CH}CH_2\overset{\overset{O}{ }}{C}NMe_2$	+9.1° (C ₆ H ₆ , 12.4) (14)
$(C_6H_5)_2CO + CH_3CH=\overset{\overset{OLi}{ }}{C}NMe_2$	10 : 1, -78, pentane	$(C_6H_5)_2\overset{\overset{OH}{ }}{C}-\underset{\underset{CH_3}{ }}{C}-\overset{\overset{O}{ }}{C}-NMe_2$	+8.5° (C ₆ H ₆ , 11.3) (~22)



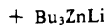
− 78, pentane



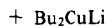
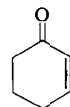
3 : 1, − 30, hexane



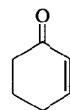
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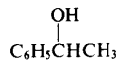
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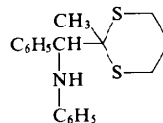
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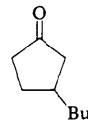
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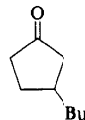
+ 4.7° (neat) (11)



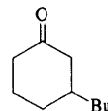
+ 15.5° (CH_2Cl_2 , 18.7)



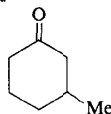
− 10° (C_6H_6 , 5.9)



+ 6.9° (C_6H_6 , 6.8)


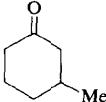

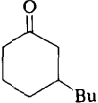
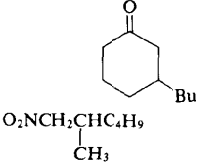
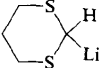
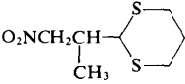
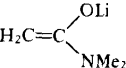
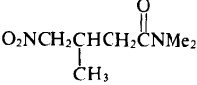


− 0.9° (C_6H_6 , 11.5)



− 1.7° (neat) (13.6)

TABLE I (Continued)

Reagents		Conditions (DDB : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, c) (%, e.e)
	+ Me_3ZnLi	10 : 1, -78, ether		-0.74° (C_6H_6 , 6)
	+ Bu_3ZnLi	10 : 1, -78, ether		-1.0° (C_6H_6 , 4.3)
$\text{CH}_3\text{CH}=\text{CHNO}_2$	+ BuLi	10 : 1, -78, pentane		+ 0.9° (C_6H_6 , 10.4) (28)
$\text{CH}_3\text{CH}=\text{CHNO}_2$	+ 	10 : 1, -78, pentane		-4.3° (C_6H_6 , 7.5) (45)
$\text{CH}_3\text{CH}=\text{CHNO}_2$	+ 	10 : 1, -78, pentane		+0.7° (C_6H_6 , 5.4) (10)

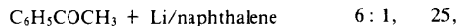
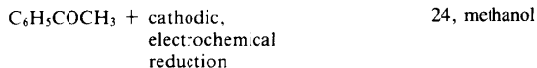
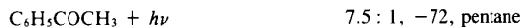
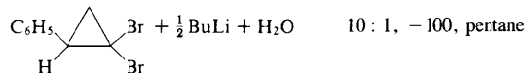
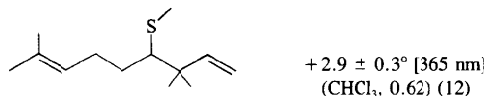
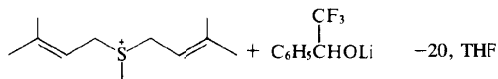
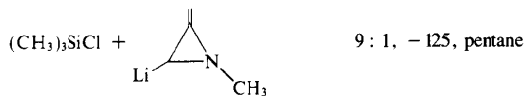


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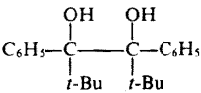
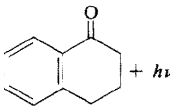
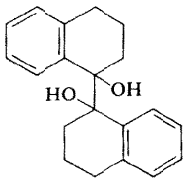

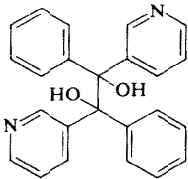
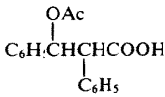
Reagents	Conditions (DDE : Reagent, Temp. °C, Solvent)	Product	$[\alpha]_D$ (Solvent, c) (%, e.e)
$C_6H_5CO-t-Bu + h\nu$	-30, neat DDB		-1.2°[(C ₂ H ₅) ₂ O, 5.0]
 $+ h\nu$	-35, pentane		+22.3° (CHCl ₃ , 5.0)
C_6H_5CO-  $+ h\nu$	-15, neat DDB		-20.0° (CH ₃ SOCH ₃ , 2.0)
$C_6H_5CHO + C_6H_5CH_2COOH +$ AcOAc	6 : 1, -25		diastereomer a +5.0°, diastereomer b +26.0° (C ₂ H ₅ OH, 3)

TABLE II
COMPARISON OF TMB^a WITH DDB^b USED AS COSOLVENTS IN THE ADDITION OF
n-BUTYLLITHIUM TO VARIOUS ALDEHYDES AT -78°C IN PENTANE³
 $\text{RCHO} + \text{C}_4\text{H}_9\text{Li} \rightarrow \text{RCH(OH)C}_4\text{H}_9$

R	e.e. (%)		Sense of Rotation, Absolute Configuration
	with TMB ^a	with DDB ^b	
CH ₃	1.2	7.5	(+)-S
C ₂ H ₅	8.8	11.5	(+)-S
<i>i</i> -C ₃ H ₇	18.0	19.0	(+)-R
<i>t</i> -C ₄ H ₉	22.8	13.5	(+)-R
(C ₂ H ₅) ₂ CH	20.0	19.0	(+)
<i>c</i> -C ₆ H ₁₁	25.0	22.5	(+)-R
C ₆ H ₅	30.0	19.0	(+)-R
4-CH ₃ -C ₆ H ₄	32.5	11.5	(+)
2-CH ₃ -C ₆ H ₄	45.3	10.5	(+)
2,4,6-(CH ₃) ₃ -C ₆ H ₂	23.0	2.3	(+)

^aTMB = (*S,S*)-(-)-1,2,3,4-tetramethoxybutane.

^bDDB = (*S,S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane.

Another chiral cosolvent, which is less readily separated from low boiling and/or water soluble products and which is somewhat less stable toward organolithium reagents, is (*S,S*)-(-)-1,2,3,4-tetramethoxybutane (TMB).³ As is shown in Table II, it is a cosolvent that is superior to DDB in differentiating between the enantiotopic faces of aldehydes with organolithium reagents.³ Finally, the octamethyl-1,4-diamino-2,3-bis(2-aminoethoxy)butane (DEB)⁵ can be used in a 2 : 1 ratio with alkylolithium reagents to produce carbinols in even higher enantiomeric yields.

DDB, TMB, and DEB are far superior to other neutral chiral auxiliary agents used in the same reactions.^{3,10-13}

1. Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092-Zürich and Institut für Organische Chemie der Justus Liebig-Universität, Giessen, Fachbereich 14, Heinrich-Buff-Ring 58, D-6300-Giessen.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); Registry Number

(*S,S*)-(+)-1,4-Bis(dimethylamino)-2,3-dimethoxybutane [DDB]: 1,4-Butanediamine-2,3-dimethoxy-*N,N,N',N'*-tetramethyl-, (*S,S*)-(+)- (8); 1,4-Butanediamine, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[*S,S*]- (9); (26549-21-3)

(*R,R*)-(+)-Tartaric acid diethyl ester; Diethyl tartrate: Tartaric acid, diethyl ester, (*R*)-(+)-; Tartaric acid, diethyl ester, (+)- (8); (608-84-4)

(*R,R*)-(+)-*N,N,N',N'*-Tetramethyltartaric acid diamide: Tartramide, *N,N,N',N'*-tetramethyl-(+)- (8); Butanediamide, 2,3-dihydroxy-*N,N,N',N'*-tetramethyl-[*R,R*]- (9); (26549-65-5)

Dimethylamine (8); Methanamine, *N*-methyl- (9); (124-40-3)

(*R,R*)-(+)-2,3-Dimethoxy-*N,N,N',N'*-tetramethylsuccinic acid diamide: Succinamide, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-(+)- (8); Butanediamide, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[*R,R*]- (9); (26549-29-1)
Benzyltriethylammonium chloride: Ammonium, benzyltriethyl-, chloride (8); Benzenemethanaminium, *N,N,N*-triethyl-, chloride (9); (56-37-1)

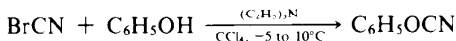
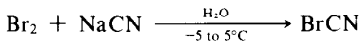
Dimethyl sulfate: Sulfuric acid, dimethyl ester (8, 9); (77-78-1)

(*R,R*)-(+)-Tartaric acid: L-(+)-Tartaric acid; (+)-Tartaric acid (8); (87-69-4)

(*S,S*)-(-)-Tartaric acid (8); Butanedioic acid, 2,3-dihydroxy-[*S,S*]- (9); (147-71-7)

CYANIC ACID ESTERS FROM PHENOLS: PHENYL CYANATE

(Cyanic acid, phenyl ester)



Submitted by D. MARTIN¹ and M. BAUER

Checked by E. R. HOLLER, JR. and R. E. BENSON

1. Procedure

Caution! These operations, which involve toxic reagents, should be conducted in an efficient hood.

A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a 200-mL pressure-equalizing dropping funnel with a stopper is charged with 160 g (50.9 mL, 1.0 mol) of bromine (Note 1) and 150 mL of water. The mixture is stirred rapidly while cooling in an ice-salt bath to -5°C , and a solution of 49.0 g (1.0 mol) of sodium cyanide in 150 mL of water is added dropwise over a 40–50 min period while maintaining the temperature of the reaction mixture at -5 to 5°C . The resulting solution is stirred an additional 5–10 min (Note 2). A solution of 89.5 g (0.95 mol) of phenol in 300 mL of tetrachloromethane (Note 3) is added in one portion to the flask. The resulting mixture is stirred vigorously while 96.0 g (131 mL, 0.95 mol) of triethylamine is added dropwise over a 30–40 min period at such a rate that the temperature does not exceed 5 – 10°C . After an additional 15 min of stirring, the mixture is transferred to a separatory funnel, the organic phase is separated and the aqueous layer is extracted twice with 50-mL portions of tetrachloromethane. The organic phases are combined and washed three times with 50-mL portions of water and then dried over polyphosphoric anhydride (Note 4). The drying agent is removed by filtration and the solvent is removed by distillation under reduced pressure using a rotary evaporator at 20°C (25 mm). A few drops of polyphosphate ester (Note 5) are added to the remaining liquid and the product is distilled through a 20-cm Vigreux column to give 85–96 g (75–85%) of phenyl cyanate,

bp 77–79° (13 mm), n_D^{20} 1.5094–1.5100, d_4^{20} 1.096. The product is a colorless liquid with a pungent odor (Note 6).

2. Notes

1. The chemicals used were commercially available products and were used without further purification. The checkers used sodium cyanide, phenol, and tetrachloromethane from Fischer Scientific Company, bromine from Matheson, Coleman and Bell, phosphoric anhydride from J. T. Baker Chemical Co., and triethylamine from Eastman Organic Chemicals.

2. The solution should develop a yellowish color.

3. The procedure can also be conducted using other water immiscible solvents such as ether, trichloromethane, and benzene.²

4. Other drying agents such as anhydrous calcium chloride can also be used. The desiccation must be done carefully since water is soluble in the product in the presence of phenol and may cause trimerization of the cyanate to a 1,3,5 triazine derivative.

5. A few drops of polyphosphate ester are a good drying agent and stabilizer.³ The ester may be prepared by heating polyphosphoric anhydride in dry ether and trichloromethane for 40 hr followed by removal of the solvent.⁴ The checkers found that the use of polyphosphate ester was essential to obtain the described yield.

6. The spectral properties of phenyl cyanate are as follows. IR(CCl_4) cm^{-1} : 2235 (m), 2261 (m), 2282 (S) ($\nu_{\text{C}\equiv\text{N}}$).⁵ UV (cyclohexane) nm max (log ϵ): 216 (3.21), 256 (2.58), 262 (2.75), and 268 (2.67).⁶ The product was further characterized by vapor phase chromatography analysis using a 200-cm column containing 10% SE 52 on Chromosorb W/AW/DMCS at 140°C with a hydrogen flow rate of 70 mL/min and a retention time of 1.47 min.

3. Discussion

Although isocyanates have been known for some time, the isomeric cyanates were unknown until 1964. The latter were first prepared almost simultaneously by two different methods: (1) thermolysis of 5-aryl- or 5-alkyloxy-1,2,3,4-thiatriazoles^{6,7} and (2) by reaction of phenols or alcohols with cyanogen halides.⁸ Since their synthesis, cyanates have ac-

quired considerable synthetic significance.⁹⁻¹⁴ The simplified procedure described here for preparation of phenyl cyanate is a combination of the preparation of cyanogen bromide¹⁵ and the cyanation of phenol in the presence of a base.⁸ This procedure is also applicable to many other phenols, bisphenols, naphthols, and some acidic alcohols. Examples are given in Table I.

Aryl cyanates have activated cyano groups and undergo many reactions.¹⁴ They are effective dehydrating and hydrogen sulfide-bonding agents in organic synthesis.^{9-11,13,14} *N*-, *O*-, and *S*-nucleophiles (HX) add to the carbon atom of the cyano group to form the corresponding carbonic

acid imide esters ($\text{ArO}-\overset{\text{X}}{\underset{|}{\text{C}}}=\text{NH}$).^{9-11,13,14} Transfer of the cyano group to a number of carbon nucleophiles also occurs.^{9-11,13,14} Acyl halides (AcCl)

add to the nitrogen atom of the cyano group to give *N*-acylated carbonic

acid imide chlorides ($\text{ArO}-\overset{\text{Cl}}{\underset{|}{\text{C}}}=\text{N}-\text{Ac}$).¹²⁻¹⁴ These compounds are useful starting materials for syntheses of heterocyclic compounds. The cyanates also undergo 1,3- and 1,4-dipolar cycloadditions involving the cyano group to give substituted azoles and azines.^{9-11,13,14} Polycyclic trimerization of dicyanates to poly-*s*-triazines is of considerable importance.¹⁶⁻¹⁸

TABLE I
CYANATES FROM HYDROXY COMPOUNDS

Hydroxy Compound	Cyanate	mp (°C) (bp, °C/mm)	Yield (%)
2-CH ₃ C ₆ H ₄ OH	2-CH ₃ C ₆ H ₄ OCN	(88–90/10)	81
4-CH ₃ C ₆ H ₄ OH	4-CH ₃ C ₆ H ₄ OCN	(90–91/10)	87
4-CH ₃ OC ₆ H ₄ OH	4-CH ₃ OC ₆ H ₄ OCN	22–26 (118–119/10)	91
2-ClC ₆ H ₄ OH	2-ClC ₆ H ₄ OCN	(112–113/13)	81
4-ClC ₆ H ₄ OH	4-ClC ₆ H ₄ OCN	38–39 (100–101/10)	87
2-CH ₃ OCOC ₆ H ₄ OH	2-CH ₃ OCOC ₆ H ₄ OCN	58–60	84
2-Naphthyl-OH	2-Naphthyl-OCN	(162–164/12)	95
4-NCOC ₆ H ₄ OH	4-NCOC ₆ H ₄ OCN	107–109	98
CCl ₃ CH ₂ OH	CCl ₃ CH ₂ OCN	(77–78/10)	75
CF ₃ CH ₂ OH	CF ₃ CH ₂ OCN	(29–30/13)	81

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Bromine (8, 9): (7726-95-6)

Sodium cyanide (8, 9); (143-33-9)

Cyanogen bromide (CNBr) (8, 9); (506-68-3)

Triethylamine (8); Ethanamine, *N,N*-diethyl- (9); (121-44-8)

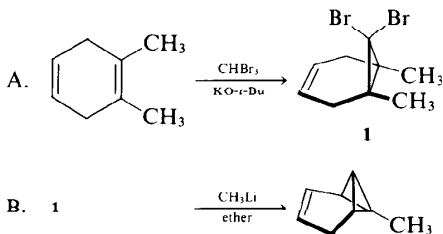
Carbon tetrachloride (8); Methane, tetrachloro- (9); (56-23-5)

Phenol (8, 9); (108-95-2)

Cyanic acid, phenyl ester (8, 9); (1122-85-6)

Phosphorus pentoxide [P_2O_5]: Phosphorus oxide (8, 9); (1314-56-3)

1,6-DIMETHYLTRICYCLO[4.1.0.0^{2,7}]HEPT-3-ENE



Submitted by R. T. TAYLOR¹ and L. A. PAQUETTE¹
 Checked by DAVID A. CORTES and M. F. SEMMELHACK

1. Procedure

A. *7,7-Dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene*. Into a 3-L, three-necked flask equipped with an overhead stirrer, 1-L addition funnel, and reflux condenser capped with a nitrogen inlet tube are introduced 44.8 g (0.4 mol) of powdered potassium *tert*-butoxide (Note 1) and 1 L of olefin-free petroleum ether (bp 35–55°C; Note 2). To this stirred mixture is added a solution containing 38.0 g (0.35 mol) of 1,2-dimethyl-1,4-cyclohexadiene (Note 3) in 200 mL of the same solvent. With external cooling from an ice bath and under nitrogen, 102.4 g (0.4 mol) of bromoform in 400 mL of petroleum ether is added dropwise during 1 hr. The ice bath is removed and the resultant slurry is stirred at room temperature under nitrogen for 6 hr. Water (500 mL) is added and the mixture is poured into a 3-L separatory funnel containing 300 mL of benzene. The organic layer is washed with four 500-mL portions of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator (Note 4). Further evacuation at 0.5 mm produces a solid which is recrystallized from ether–petroleum ether (1 : 3) to afford 55–62 g (56.5–63.5%) of colorless solid, mp 95–98°C (Note 5).

B. *1,6-Dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene*. A solution of 20.95 g (0.075 mol) of 7,7-dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene in 500 mL of anhydrous ether is placed in a 1-L, three-necked flask equipped with a magnetic stirring bar, reflux condenser, addition funnel, and nitrogen inlet tube. With stirring under nitrogen and external cooling in an

ice bath, 50 mL of 1.6 *M* ethereal methyllithium (Note 6) in 70 mL of ether (0.08 mol) is introduced by dropwise addition during 30 min. The ice bath is removed and the mixture is stirred at room temperature for 1 hr. After 100 mL of water has been cautiously introduced, the mixture is transferred to a separatory funnel and the organic layer is separated. This solution is washed with water (3×100 mL), dried over anhydrous sodium sulfate (Note 7), and carefully concentrated by slow distillation through a 40-cm Vigreux column at atmospheric pressure, heating at $<60^{\circ}\text{C}$ (Note 8). The residual liquid is distilled through a short, unpacked column to give 4.2–4.4 g (46–49%) of colorless oil, bp $48\text{--}49^{\circ}\text{C}$ (23 mm) (Note 9). Under the proper conditions, this hydrocarbon can be stored for 2 weeks at -5°C without deterioration.

2. Notes

1. Potassium *tert*-butoxide can be obtained commercially from MSA Research Corporation, Callery, Pennsylvania. The checkers used a sample from Aldrich Chemical Company, Inc.

2. A liter of technical grade petroleum ether was treated in a separatory funnel with 200 mL of concentrated sulfuric acid, washed with water, and dried over anhydrous magnesium sulfate.

3. This diene was prepared by the procedure of Paquette and Barrett²; satisfactory results can be realized with material of 70–85% purity (15–30% contamination by *o*-xylene) since the aromatic impurity does not react subsequently and is easily removed.

4. Any residual *o*-xylene should be removed prior to crystallization because the dibromide is exceedingly soluble in aromatic solvents.

5. Further recrystallization is not necessary, but pure crystals, mp $107\text{--}108^{\circ}\text{C}$, can be obtained in the manner described by Vogel and co-workers.³

6. The ethereal methyllithium solutions were purchased from Alfa Inorganics. The concentration of methyllithium in such solutions may be conveniently determined by a procedure described elsewhere^{4,5} in which the lithium reagent is titrated with *sec*-butyl alcohol, utilizing the charge transfer complex formed from bipyridyl or *o*-phenanthroline and the lithium reagent as indicator.

7. Anhydrous magnesium sulfate is too acidic for this purpose and promotes rearrangement of the hydrocarbon.

8. All glassware that is to contain the cyclized product should be washed in base and dried (where necessary) prior to use.

9. The checkers found bp $55\text{--}56^{\circ}\text{C}/30$ mm. Attempted distillation at

ca. 50 mm (bp 75°C) led to significant rearrangement to a dimethylcycloheptatriene. The product exhibits the following ¹H NMR spectrum (CDCl₃) δ: 1.08 (s, 3 H, CH₃), 1.33 (d, 1 H, *J* = 2, methine C—H), 1.52 (s, 3 H, CH₃), 2.15–1.80 (m, 3 H, allylic methylene and methine), 5.50–5.15 (m, 1 H, olefinic C—H), 6.10–5.70 (m, 1 H, olefinic C—H).

3. Discussion

The tricyclo[4.1.0.0^{2,7}]hept-3-ene ring system, with its conjugated bicyclobutane ring and double bond and its isomeric relationship to cycloheptatriene, has recently commanded attention as a precursor of yet more highly strained molecules. However, the preparation of the parent hydrocarbon by reaction of 7,7-dibromo-3-norcarene with methyllithium at 0°C, first reported by Klumpp and Vrielink,⁶ does not proceed in yields above 1–5%.^{6,7} Placement of a single methyl group at a ring juncture position of the transient norcarenylidene intermediate is, however, adequate to promote efficient ring closure through C—H alpha insertion.^{7,8} The procedure described above is exemplary. Although two alternative routes to tricyclo[4.1.0.0^{2,7}]hept-3-enes are currently available,^{6,9} alkyl-lithium-promoted cyclization of readily available 7,7-dibromobicyclo[4.1.0]hept-3-enes constitutes the most direct and efficient approach. In addition, this procedure illustrates an entirely general method for converting norcarane derivatives to *endo,endo*-1,3-bridged bicyclobutanes.^{10–12}

Exposure of tricyclo[4.1.0.0^{2,7}]hept-3-enes to catalytic amounts of Ag⁺ leads instantaneously and quantitatively to cycloheptatriene derivatives.⁷ Promise of their usefulness as synthetic intermediates is growing rapidly.^{13,14}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,6-Dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (9); (—)

Methyl lithium (8, 9); (917 54 4)

1,2-Dimethyl-1,4-cyclohexadiene: 1,4-Cyclohexadiene, 1,2-dimethyl- (8, 9); (17351-28-9)

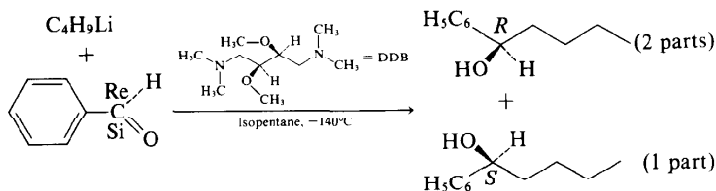
7,7-Dibromo-1,6-dimethylbicyclo[4.1.0]hept-3-ene: Bicyclo[4.1.0]hept-3-ene, 7,7-dibromo-1,6-dimethyl- (9); (38749-43-8)

Bromoform: Methane, tribromo- (8, 9); (75-25-2)

ENANTIOSELECTIVE ADDITION OF BUTYL LITHIUM IN THE PRESENCE OF THE CHIRAL COSOLVENT DDB.

(+)-(R)-PHENYL-1-PENTANOL

[Benzenemethanol, α -butyl-, (R)-]



Submitted by DIETER SEEBACH and AUGUST HIDBER¹
Checked by M. F. SEMMELJACK and CHARLES SHUEY

1. Procedure

As shown in Figure 1, a dry, 1-L, three-necked flask is equipped with an overhead stirrer bearing a four-bladed propeller of ca. 2.5-cm diameter

driven by a strong, safely connected motor A (Note 1), a rubber septum, and a three-way stopcock. The air in the flask is replaced by dry argon or nitrogen, the pressure of which is maintained during the reaction at ca. 50 mm above atmospheric pressure with a mercury bubbler (Note 2). A second stirrer (motor B, Figure 1) to agitate the baths is attached next to the flask with the propeller just below the bottom of the flask. Finally, a 4.5- × 20-cm test tube is held next to the bath stirrer. The entire apparatus (Figure 1) is mounted well above the bench to allow for immersion of the flask, bath stirrer, and tube into cooling baths and for exchange of bulky bath containers with the aid of a lab-jack. The flask

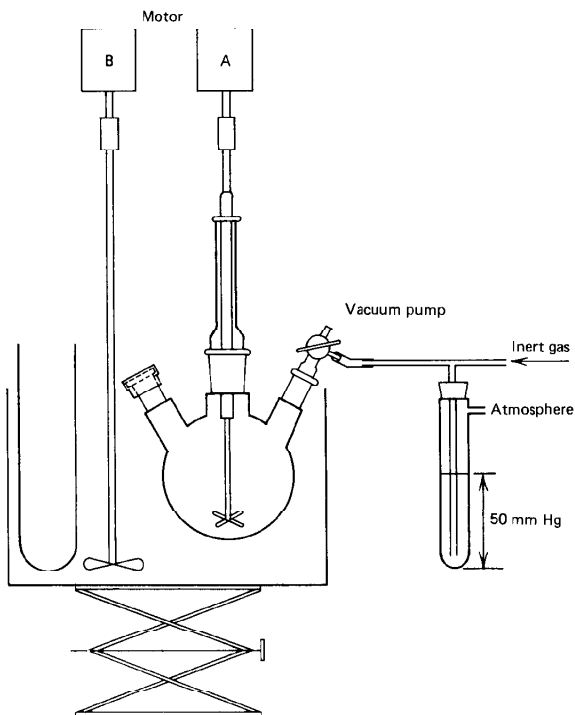


Figure 1

is charged (Note 3) with 400 mL of 2-methylbutane (isopentane) (Note 4) and 24.6 g (27.5 mL, 0.12 mol) of (*S,S*)-(+) -*N,N,N',N'*-tetramethyl-1,4-diamino-2,3-dimethoxybutane (DDB) (Note 5). A methanol-dry ice bath is raised to immerse the flask and cool the contents to -78°C with slow stirring, whereupon 0.021 mol of butyllithium (13.5 mL of a 1.56 *M* solution in hexane) (Note 6) is added within a few minutes. A second cooling bath is prepared in a ca. 7-L Dewar cylinder (Note 7) by pouring liquid nitrogen into a stirred (glass rod) mixture of methylcyclohexane/isopentane (3 : 2) (Note 8) until about half of the liquid has solidified and a slush has been formed, the temperature of which is ca. -140°C (Note 9). The reaction flask is cooled to the lower temperature by exchanging baths and waiting for 15 min with bath stirring. The bath is temporarily lowered and cooled until again half frozen by pouring in liquid nitrogen with manual agitation (Note 10). From now on, cooling is kept constant by filling the tube in the stirred bath at intervals with liquid nitrogen (Note 10). A solution of 2.12 g (0.020 mol) of benzaldehyde (Note 11) in 20 mL of isopentane (Note 4) is added dropwise (Note 12) over 15 min to the vigorously stirred (ca. 1000 rpm) reaction mixture. After completion of the addition (ca. 0.5 hr), the bath is removed, the flask is warmed to ca. 0°C (Note 13), and the contents are poured into a 1-L separatory funnel containing 150 mL of ice-cold 2 *N* aqueous hydrochloric acid. The aqueous layer is extracted twice with 70 mL of hexane and saved for recovery of the chiral auxiliary agent DDB (Note 14). The combined organic layers are sequentially washed with saturated aqueous bicarbonate and sodium chloride solutions and concentrated in a rotary evaporator to ca. 200 mL. The solution is then transferred to a 500-mL separatory funnel and vigorously shaken with 40 mL of a saturated aqueous sodium bisulfite solution to precipitate the bisulfite adduct of unreacted benzaldehyde (Note 15). After filtration (if necessary) the residue and the aqueous phase are washed with hexane. The combined organic solution is dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. Simple distillation yields 2.60–2.95 g (80–90%) of 1-phenyl-1-pentanol, bp $54\text{--}56^{\circ}\text{C}$ (0.02 mm) $[\alpha]_{\text{D}} = 6.13^{\circ}$ (neat) (Note 16), optical yield 30% (Note 17).

2. Notes

1. The checkers used a conventional, flat, crescent-shaped Teflon blade, 8 cm long.

2. This is done as previously described in *Organic Syntheses* procedures: Seebach, D.; Beck, A. K. *Org. Synth.* **1971**, *51*, 39, 76; Enders, D.; Pieter, R.; Seebach, D. *Org. Synth.* **1978**, *58*, 113. All connections should be securely fastened.

3. All additions of solvents and reagents are carried out through the rubber septum with dry, appropriately sized, and argon-flushed syringes with hypodermic needles. Because of its low boiling point, it is advantageous to force isopentane into the 100-mL syringe by applying pressure to the storage flask.

4. Isopentane (bp 28°C, ~95% 2-methylbutane), was purchased from Fluka AG, freshly distilled from P₂O₅, and stored under inert gas pressure.

5. DDB is presently available from Aldrich Chemical Company, Inc. For its preparation, see the accompanying procedure: Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. *Org. Synth.* **1982**, *61*, previous prep 2097. DDB is hygroscopic and must be refluxed for some time and freshly distilled from lithium aluminum hydride (bp 38°C/0.01 mm) prior to use. The submitters used material with $[\alpha]_D$ 14.7°; the checkers' sample showed $[\alpha]_D$ 14.3°.

6. Butyllithium was purchased from Metallgesellschaft, Frankfurt, and titrated for active alkylolithium using diphenylacetic acid as an indicator: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

7. If no such Dewar container is available, two appropriately sized plastic buckets with a layer of styrofoam particles between the inner and outer bucket can be used.

8. The mixture was used as purchased from Fluka AG. The submitters have occasionally used, as a bath liquid, petroleum ether (bp 40–60°C) of unknown composition or pure isopentane (mp –160°C). In such cases, temperature control is necessary; it was achieved with a platinum temperature sensor inside the reaction mixture.

9. The checkers used a thermocouple to verify the temperature of the cooling bath.

10. The coolant must not be poured directly into the bath, because local overcooling can cause partial freezing of the reaction mixture, which is clear and homogeneous before addition of the aldehyde. If freezing should occur, the flask is temporarily warmed slightly by removing the bath.

11. Benzaldehyde was obtained from Fluka AG or Aldrich Chemical Company, Inc., and freshly distilled under reduced pressure (40°C/3 mm).

12. Clear drops of the aldehyde solution must fall from the tip of the

needle directly into the reaction mixture. If the needle is inserted too far, the aldehyde can freeze and clog the needle; it is thawed by extracting the needle tip into the upper, warmer part of the neck.

13. A slow method is to wait until the ice that has condensed on the walls of the flask has all melted. Alternatively, the flask may be immersed in a methanol bath.

14. The combined aqueous layers of several runs are saturated with potassium hydroxide by adding KOH pellets with cooling. DDB separates on top of the aqueous phase and is extracted with ether. Distillation leads to ~90% recovery (bp 42–43°C/0.05 mm).

15. The checkers observed no precipitate formation at this point.

16. In five runs carried out by the submitters at temperatures between –140 and –150°C, the specific rotations of phenylpentanol (d_4^{20} 0.967) ranged from $[\alpha]_D$ 5.95 to 7.0° (29–34% optical yield; see Note 17). At dry ice temperature, the optical yields are only half as high.² The checkers obtained specific rotations of $[\alpha]_D$ 5.87° and 6.05° (28 and 29% optical yield).

17. For optically pure 1-phenyl-1-pentanol a specific rotation of $[\alpha]_D^{25}$ 20.7° (neat) is reported.³

3. Discussion

The optically active form of 1-phenyl-1-pentanol has been prepared by a variety of methods.^{4,5} The present procedure is a modification and extended description of our previously published² chiral solvent method. DDB and other auxiliary agents from tartaric acid lead to a wide range of optically active products from achiral components with prochiral centers (enantioselective syntheses). A list of examples of DDB applications is found in the accompanying procedure describing its preparation from tartaric acid.

1. Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.
2. Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301; Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1701, 1710; Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695.
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Differentiating Reactions," Academic Press: New York, 1977; (c) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-(R)-1-Phenyl-1-pentanol: Benzenemethanol, α -butyl-, (R)-; (19641-53-3)

n-Butyllithium: Lithium, butyl (8, 9); (109-72-8)

(S,S) (+) *N,N,N',N'*-Tetramethyl-1,4-diamino-2,3-dimethoxybutane [DDB]: 1,4-Butanediamine-2,3-dimethoxy-*N,N,N',N'*-tetramethyl-, (S,S)- (1)- (8); 1,4-Butanediamine, 2,3-dimethoxy-*N,N,N',N'*-tetramethyl-[S-(*R*,R**)]- (9); (26549-21-3)

Benzaldehyde (8, 9); (100-52-7)

Phosphorus pentoxide [P₂O₅]: Phosphorus oxide (8, 9); (1314-56-3)

Lithium aluminum hydride: Aluminate(1-), tetrahydro-, lithium (8); Aluminate(1-), tetrahydro-, lithium, (T-4)- (9); (16853-85-3)

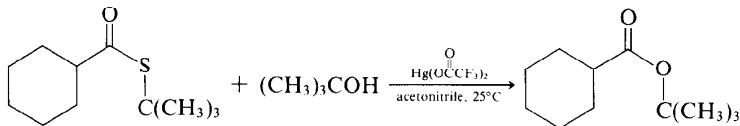
Diphenylacetic acid: Acetic acid, diphenyl- (8); Benzeneacetic acid, α -phenyl- (9); (117-34-0)

1-Phenyl-1-pentanol: Benzenemethanol, α -butyl- (9); (583-03-9)

(S)-1-Phenyl-1-pentanol: Butanemethanol, α -butyl-, (S)- (9), (33652-83-4)

PREPARATION OF *O*-ESTERS FROM THE CORRESPONDING THIOL ESTERS

(Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester)



Submitted by WAN KIT CHAN,¹ S. MASAMUNE,¹ and GARY O. SPESSARD²

Checked by TRINA KITTREDGE and ROBERT V. STEVENS

1. Procedure

A 500-mL, round-bottomed flask equipped with a magnetic stirring bar is flushed with nitrogen. The flask is then charged with 5.56 g (0.028 mol) of *S*-*tert*-butyl cyclohexylmethanethioate (Note 1), 5.55 g (0.075 mol) of *tert*-butyl alcohol, and 250 mL of anhydrous acetonitrile (Note 2). The mixture is stirred vigorously and 23.7 g (0.056 mol) of mercury(II) trifluoroacetate (Note 3) is added in one portion. The resulting mixture is stirred vigorously for 45 min and then concentrated to approximately 50–75 mL on a rotary evaporator (Note 4). To this concentrated mixture is added 250 mL of hexane and the orange solid that forms is removed by filtration. The filter pad is then washed with 50 mL of hexane. The filtrate and washings are combined and washed with a 50 mL portion of aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give a pale yellow liquid (Note 4).

The crude product is purified by passing it through a column (4.5 cm × 30 cm) of neutral alumina (Note 5) using chloroform as eluant. The desired product moves with the solvent front, and the first 300–350 mL of eluant contains all of the product. Removal of the solvent gives 4.96 g. The product, which contains a small amount of *tert*-butyl alcohol, can be further purified by distillation through a short-path apparatus to give 4.6 g (90%) of pure *O*-ester, bp 91°C (25 mm) (Notes 4 and 6).

2. Notes

1. This reagent is prepared according to *Org. Synth.*, **1982**, 61, 134.
2. Acetonitrile, obtained from J. T. Baker Chemical Co., was refluxed overnight with phosphorus pentoxide and then distilled under nitrogen onto freshly activated Linde 4A molecular sieves. The acetonitrile was stored over the molecular sieves for 24 hr before use.
3. Although mercury(II) trifluoroacetate may be obtained commercially, the submitters recommend that it be freshly prepared. A mixture of red mercury(II) oxide (108.3 g, 0.5 mol) (obtained from BDH Chemicals Ltd.) and freshly distilled trifluoroacetic acid (137.0 g, 1.2 mol) (purchased from J. T. Baker Chemical Co.) was heated at 80°C for 30 min. The excess trifluoroacetic acid and the water formed in the reaction were removed under reduced pressure. The white crystalline residue was then dried (50°C, 0.01 mm) for 48 hr to give a quantitative yield of product.
4. The temperature of the water bath was kept below 28°C during evaporation of the acetonitrile.
5. Woelm neutral alumina, activity grade 1, (300 g) was used. The column was packed using hexane.
6. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 1735 (strong); ^1H NMR (CDCl_3) δ : 1.38 [singlet, 9 H, $\text{C}(\text{CH}_3)_3$] 1.0–2.4 (multiplet, 11 H, cyclohexane protons).

3. Discussion

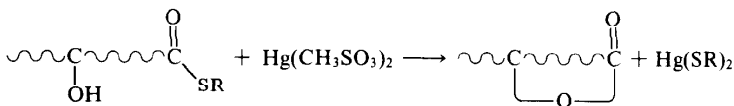
In recent years much attention has been directed toward efficient ester (and lactone) formation in connection with the synthesis of naturally occurring macrolides.^{3,4} Four principal methods for such a reaction have emerged from these studies:

Method 1. Use of a thiophilic metal ion to activate an alkane- or arenethiol ester for nucleophilic displacement by an alcohol is applicable to both ester and lactone formation.⁵

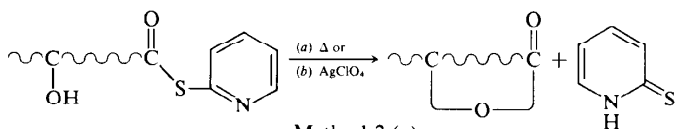
Method 2. Corey's "double activation" method for lactone formation is patterned after Mukaiyama's procedure for peptide formation and involves refluxing a solution of the 2-pyridinethiol ester of a hydroxy acid in a high-boiling solvent for a prolonged period of time.⁶

Method 3. Gerlach's modification of Method 2 uses AgClO_4 or AgBF_4 to catalyze the cyclization.⁷

Method 4. Mitsunobu's method uses a combination of diethyl azodicarboxylate and triphenylphosphine as a condensing agent.⁸



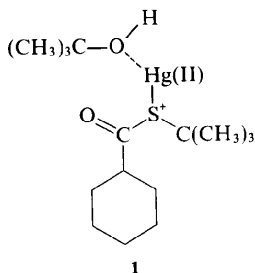
Method 1



Method 2 (a)

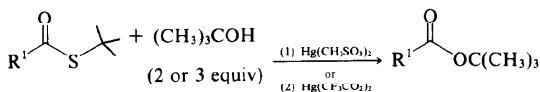
Method 3 (b)

Method 1 offers some distinct advantages. First, an ester such as the 1,1-dimethylethylthiol ester serves as an excellent protective group, surviving both relatively mild alkaline and acid conditions, and has been used successfully in the synthesis of many macrolide natural products.^{4b,g,j,n,o,q} Second, reaction of a metal ion such as $\text{Hg}(\text{II})$ with the thiol ester formally creates a highly reactive trivalent sulfur species, and thus ester (and lactone) formation proceeds very rapidly at room temperature or below. More importantly, bulky substituents or double bonds located near the reaction centers (i.e., near the hydroxy and acyl groups) do not impede the reaction (see Table I).⁴ⁱ Thus *tert*-butyl pivalate and *tert*-butyl crotonate are prepared in excellent yields. In the absence of alcohols, *tert*-butyl cyclohexanemethanthioate reacts with $\text{Hg}(\text{CF}_3\text{CO}_2)_2$ to form cyclohexanecarboxylic trifluoroacetic anhydride. Reaction of this anhydride with *tert*-butyl alcohol to give the ester, however, proceeds ca. 10 times more slowly than the $\text{Hg}(\text{II})$ -catalyzed ester formation described above.⁹ The intermediacy of the corresponding ketene has been eliminated by use of an appropriately deuterated compound⁹ and pivalic acid. Thus the metal-catalyzed ester formation appears to proceed for the most part through coordination of the alcohol to the metal, as shown in a possible intermediate (**1**), followed by collapse into the ester and mercuric salts with retention of stereochemistry at the carbon atom alpha to the carboxy group.



This method is not free from disadvantages: the electrophilicity of Hg(II) toward reactive alkanes may sometimes be a problem. However, in most cases the reactivity of Hg(II) with sulfur significantly exceeds that with ordinary or electron-deficient ($\text{C}=\text{C}-\text{C}=\text{O}$) double bonds, and other combinations of thiol esters and thiophilic metals may be used to overcome this problem. The more acidic the reacting thiol, the less thiophilic is the metal needed to effect the reaction, and in some cases Cu(I), Cu(II), and Ag(I) are superior to Hg(II). For example, the combination of $\text{Ag(I)CF}_3\text{CO}_2$ [but not Ag(I)ClO_4 or Ag(I)BF_4] and a benzene-thiol ester is very efficient for ester formation. The presence of electron-withdrawing groups such as the $\text{C}=\text{C}$ bond and protected hydroxy groups

TABLE I

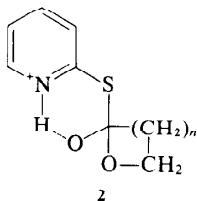


R^1	Reagent	Buffer	Yield (%) ^a
$\text{c-C}_6\text{H}_{11}-$	1 or 2	Na_2HPO_4 (or none)	100
$(\text{CH}_3)_3\text{C}-$	1	-CH ₂ Cl	90
$(E)-\text{CH}_3\text{CH}=\text{CH}-$	1 or 2	-CH ₂ Cl	85
$(Z)-\text{CH}_3\text{CO}_2\text{C}(\text{CH}_3)=\text{CH}-$	1	Na_2HPO_4	90

^a The yields are estimated by GC analysis.

somewhat retards the ester formation. A few examples are shown in Table II.^{4j} All these observations appear to conform with the hard and soft acid and base principle of Pearson. Further, it is clear that Gerlach's report of the use of Ag(I) to activate 2-pyridinethiol esters (Method 3) is fully in accord with this trend.

Corey's "double activation" procedure (Method 2) does not use an external reagent to activate the functional group, but effects cyclization by heating a solution of the 2-pyridinethiol ester of a hydroxy acid for a prolonged period. Several pieces of evidence point to the intermediacy of **2** in this lactonization.¹⁰ If one accepts this intermediate, it follows that a hydroxy(2-pyridinethiol) ester, heavily substituted near the reaction centers (i.e., near the hydroxyl and acyl groups), would encounter a high

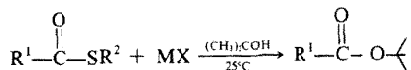


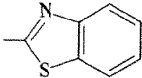
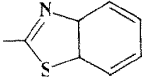
energy barrier in the process leading to **2**. This inference has been confirmed by measuring the approximate rates of reaction of 2-pyridine- and 2-benzothiazolethiol esters of cyclohexanecarboxylic acid with primary, secondary, and tertiary alcohols.^{3a,9} This steric retardation of the reaction may constitute a major drawback to Method 2. A marked improvement has been made, however, and the latest version of this method¹¹ involves use of the 1-methyl- or 1-isopropyl-4-*tert*-butylimidazole-2-thiol ester of the hydroxy acid which undergoes cyclization ~ 100 times faster than the corresponding 2-pyridinethiol ester. This improved method has been used in syntheses of erythronolide A^{4m} and B.^{4k}

Lactonization of aliphatic hydroxy acids proceeds with the aid of two reagents, diethyl azodicarboxylate and triphenylphosphine. This fourth procedure has been selected as a method of choice for the final cyclization to yield vermiculine⁴ⁱ and pyrenophorin.⁴ⁿ

Several other methods to effect ester and lactone formation are now available. Mukaiyama uses 2-chloro-*N*-methylpyridinium iodide and its derivatives as a condensing agent.¹² Staab's imidazole method,¹³ suc-

TABLE II



R^1	R^2	MX	Solvent	Time	Yield (%)
<i>c</i> -C ₆ H ₁₁ —	—C ₆ H ₅	Cu(CF ₃ SO ₃)	C ₆ H ₆ /THF	10 min	95
<i>c</i> -C ₆ H ₁₁ —		Ag(CF ₃ CO ₂)	C ₆ H ₆	10 min	100
(<i>E</i>)-CH ₃ CH=CH—	—C ₆ H ₅	Cu(CF ₃ SO ₃)	C ₆ H ₆ /THF	5 hr	80
(<i>E</i>)-C ₆ H ₅ CH=CH—	—C ₆ H ₅	Cu(CF ₃ SO ₃) ₂	CH ₃ CN	1.5 hr	24
		Ag(CF ₃ CO ₂)	C ₆ H ₆ (Δ)	1.5 hr	100
		AgBF ₄	C ₆ H ₆ (Δ)	1 hr	<5
C ₆ H ₅ —		Ag(CF ₃ CO ₂)	C ₆ H ₆ (Δ)	1.5 hr	100
		Cu(CF ₃ SO ₃)	C ₆ H ₆ /THF	5 hr	90
		Cu(CF ₃ SO ₃) ₂	CH ₃ CN	30 min	100

cessfully utilized in a synthesis of pyrenophorin^{4c} and a model study for erythronolide B,¹⁴ requires a catalytic amount of strong base, and thus is applicable only to compounds stable under such conditions. The mixed anhydride of a hydroxycarboxylic acid and 2,4,6-trichlorobenzoic acid is efficiently cyclized to provide the corresponding lactone.^{41,15} Similarly, the use of a reactive phosphoric acid anhydride intermediate is equally effective.¹⁶ Some other methods for carboxyl activation have also appeared recently.¹⁷

The above discussion is a summary of the lactonization methods known at present; newer methods continue to be explored. The selection of a method for an individual case depends to a large extent on the structure and functionalities of the substrate. Detailed comments in this respect are reserved until more information has accumulated.

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Appendix

Chemical Abstracts Nomenclature (Collective Volume Number); (Registry Number)

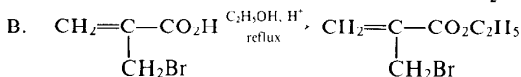
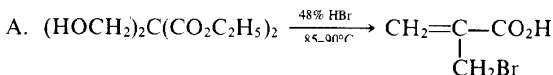
Cyclohexanecarboxylic acid, 1,1 dimethylethyl ester: Cyclohexanecarboxylic acid, *tert*-butyl ester (8); Cyclohexanecarboxylic acid, 1,1-dimethylethyl ester (9); (16537-05-6)

S-tert-Butyl cyclohexylmethanethioate: Cyclohexanecarbothioic acid, *S*-(1,1-dimethylethyl) ester (9); (54829-37-7)

Mercury(II) trifluoroacetate: Acetic acid, trifluoro-, mercury(2+) salt (8, 9); (13257-51-7)

Red mercury(II) oxide: Mercury oxide (8, 9); (21908-53-2)

ETHYL α -(BROMOMETHYL)ACRYLATE
(2-Propenoic acid, 2-(bromomethyl)-,ethyl ester)



Submitted by K. RAMARAJAN, K. RAMALINGAM, D. J. O'DONNELL, and K. D. BERLIN¹
 Checked by H. S. SHOU, E. TSOU, R. A. HAYES, and ORVILLE L. CHAPMAN

1. Procedure

A. α -(Bromomethyl)acrylic acid. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer, fraction collector, cold-finger condenser, and two thermometers. Into the flask are placed 55.0 g (0.25 mol) of diethyl bis(hydroxymethyl)malonate (Note 1) and 142 mL (1.25 mol) of 47–49% hydrobromic acid (Note 2). The mixture is then heated and the temperature of the liquid maintained between 85–90°C. A mixture of ethyl bromide and water distills during the course of 1.5–2 hr. The residue is then boiled for 10 hr, maintaining the temperature between 85–90°C (Note 3). At the end of this period, the mixture is concentrated on a rotary evaporator at 65–70°C (10–15 mm). About 100 mL of water is removed. The residue is cooled in the refrigerator overnight. Crystals of α -(bromomethyl)acrylic acid are filtered in the cold (Note 4) to give, after drying (Note 5), 17.9 g (43%) of acid, mp 71–73°C (Note 6).

B. Ethyl α -(bromomethyl)acrylate. In a nitrogen-flushed, 1-L, round-bottomed flask equipped with a magnetic stirrer, Dean Stark trap, and condenser are placed 42.0 g (0.25 mol) of α -(bromomethyl)acrylic acid and 300 mL of benzene. Approximately 50 mL of a binary azeotrope of benzene and water is distilled (Note 7). The Dean–Stark trap is removed and 100 mL of absolute ethanol (Note 8) and 1 mL of concentrated sulfuric acid are added slowly. The contents of the flask are boiled in a nitrogen atmosphere for 36 hr, the condensate being passed through 100 g of molecular sieves (Linde 3A) before being returned to the flask. About 125 mL of a mixture of benzene and ethanol is removed from the reaction

mixture by distillation (at 67°C). Then 100 mL of benzene is added and another 125 mL of benzene-ethanol mixture distilled (67–75°C). The residue is poured into 200 mL of water and neutralized with solid sodium bicarbonate (ca. 10–15 g) until CO_2 evolution ceases. The resulting solution is extracted with three 75-mL portions of ether, and the combined extracts are dried over anhydrous sodium sulfate for 3 hr. The ether is removed under reduced pressure in a rotary evaporator, and crude ester distilled to give a fraction at 39–40°C (0.9 mm) which weighs 33–34 g (71%). The ester is of high purity, as evidenced by spectral analysis (Note 9).

2. Notes

1. The checkers prepared this ester on a 0.7-mol scale by a modification of the previously published method.² The modification was effected as follows. The ethereal extract from the formaldehyde-diethyl malonate reaction, after drying over sodium sulfate for 3 hr, was concentrated in a rotary evaporator and the residue was stored in a refrigerator overnight. The crude ester was obtained as white crystals, mp 47–50°C; yield 85.6%. The checkers found that the ester prepared in this manner gave superior yields of the acrylic acid.

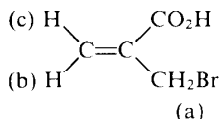
2. The submitters reported that the use of excess hydrobromic acid resulted in the formation of a mixture of dibromoisobutyric acid and α -(bromomethyl)acrylic acid as evidenced by NMR analysis.

3. Temperatures higher than 85–90°C gave a mixture of dibromoisobutyric acid and α -(bromomethyl)acrylic acid.

4. This was done at 4°C to improve the yield; otherwise considerable amounts of α -(bromomethyl)acrylic acid remain in solution.

5. The compound was air-dried for 3 days at room temperature.

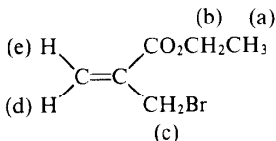
6. The product was almost pure. It could be recrystallized from Skellysolve-B (bp 60–80°C) and further purified by sublimation, mp 73–75°C (Anal. Calcd. for $\text{C}_4\text{H}_5\text{BrO}_2$: C, 29.12; H, 3.05. Found: C, 29.07; H, 3.10). IR (KBr) cm^{-1} : 1689 ($\text{C}=\text{O}$), 1626 ($\text{C}=\text{CH}_2$); ^1H NMR (CDCl_3) δ : 4.18 (s, 2 H, H_a), 6.09 (s, 1 H, H_b), 6.49 (s, 1 H, H_c).



7. There was only about 1 mL of water in the distillate.

8. Absolute alcohol was prepared by boiling commercial absolute alcohol over magnesium turnings for 4 hr in a nitrogen atmosphere.

9. The spectral properties of ethyl α -(bromomethyl)acrylate are as follows: $^1\text{H NMR}$ (CDCl_3) δ : 1.26–1.40 (t, 3 H, H_a), 4.16–4.38 (quintet, 2 H, H_b), 4.19 (s, 2 H, H_c), 5.96 (s, 1 H, H_d), 6.32 (s, 1 H, H_e).



3. Discussion

The procedure described here is a modification of that of Ferris.³ The overall yield has been increased from 17 to 30% by making changes as indicated in Notes 2 and 3. In addition, the number of stages in the preparation of ethyl α -(bromomethyl)acrylate from diethyl malonate has been reduced from four to three.

Ethyl α -(bromomethyl)acrylate has proved to be an excellent reagent for conversion of aldehydes and ketones, both acyclic and cyclic, into the corresponding α -methylene- γ -butyrolactone derivatives⁴⁻⁹ in a Reformatsky type reaction. The yield was excellent in the case of several spiro α -methylene- γ -butyrolactones.¹⁰ Synthetic α -methylene- γ -butyrolactone derivatives have been shown to possess antitumor activity.^{5,6,7,11,12} Ethyl α -(bromomethyl)acrylate has also proven of value in the synthesis of alkylated products of enol ethers of cyclohexane-1,3-dione.¹³

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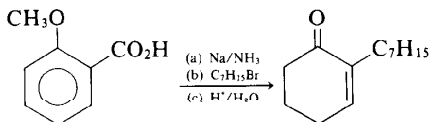
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl α -(bromomethyl)acrylate: Acrylic acid, 2-(bromomethyl)-, ethyl ester (8); 2-Propenoic acid, 2-(bromomethyl)-, ethyl (9); (17435-72-2)
Diethyl bis(hydroxymethyl)malonate: Malonic acid, bis(hydroxymethyl)-, diethyl ester (8); (20605-01-0)

2-HEPTYL-2-CYCLOHEXENONE: ALKYLATION OF THE ANION FROM BIRCH REDUCTION OF *o*-ANISIC ACID



Submitted by D. F. TABER, B. P. GUNN, and I-CHING CHIU¹

Checked by M. F. SEMMELHACK and E. STELTER

1. Procedure

Caution! Liquid ammonia should be used only in a well-ventilated hood.

2-Heptyl-2-cyclohexenone. A 1 L, three necked, round-bottomed flask is charged with 15.2 g (0.1 mol) of *o*-anisic acid (Note 1) and 100 mL of tetrahydrofuran (Note 2). An acetone-dry ice condenser and mechanical stirrer are put in place, the flask is immersed in an acetone-dry

ice bath, and 400 mL of ammonia is distilled in (Notes 3, 4). The resulting thick white suspension (the ammonium salt of the acid) is stirred mechanically. Sodium, washed sequentially with xylenes and ether, is added in small pieces. The suspension dissolves to give a pale yellow solution which, upon introduction of more sodium, changes to the characteristic blue color of excess sodium. When the deep blue color persists, a mixture of 1-bromoheptane (21.49 g, 0.12 mol) and 1.0 mL (2.4 mmol) of 1,2-dibromoethane is added in one portion. The blue color is discharged immediately, leaving a yellow solution. The acetone-dry ice bath and the condenser are removed, and the ammonia is allowed to evaporate under a gentle stream of nitrogen.

The residue is diluted with 700 mL of water, and the resulting aqueous solution is washed with three 40-mL portions of dichloromethane, acidified with cold concentrated HCl, and extracted with five 40-mL portions of 1,2-dichloroethane. The combined 1,2-dichloroethane extracts are placed in a 500-mL, one-necked, round-bottomed flask bearing a reflux condenser; water (50 mL), concentrated HCl (50 mL), and hydroquinone (300 mg) are added; and the mixture is heated at reflux under a positive pressure of nitrogen for 30 min. The mixture is cooled to 25°C, the layers are separated, and the organic layer is washed with 60 mL of 0.5 *M* aqueous sodium bicarbonate solution. The organic phase is dried over anhydrous potassium carbonate, concentrated by rotary evaporation at aspirator vacuum, and distilled through a 10-cm Vigreux column to yield a center cut, bp 100–104°C (0.02 mm), 9.0–11.5 g (46–59%) (Notes 5, 6).

2. Notes

1. *o*-Anisic acid was obtained from Aldrich Chemical Company, Inc.
2. Tetrahydrofuran was dried and made oxygen-free by boiling over sodium/benzophenone ketyl under argon, and distilling just before use.
3. Reduction in refluxing liquid ammonia (–33°C) led to substantial cleavage of the methoxyl group with resultant formation of alkylated dihydrobenzoic acid.
4. Arrangements for cooling or condensing the liquid ammonia over sodium in a preliminary drying operation could be made, but were not necessary. The results reported here were achieved by simply passing ammonia gas from a cylinder into the cold reaction system through heavy Tygon tubing.

5. The spectral properties of 2-heptyl-2-cyclohexenone are as follows: IR (CCl_4) cm^{-1} : 2920, 2860, 1670, 1455, 1435, 1370, 1170, 1120, 1095, 905; ^1H NMR (CDCl_3) δ : 0.85 (br t, 3 H, $J = 7$), 1.28 (br s, 10 H), 1.8–2.6 (m, 8 H), 6.70 (br s, 1 H); n_D^{26} 1.4738.

6. Before distillation, the crude enone contained substantial amounts of the β,γ -isomer. As an alternative to equilibration on distillation, this mixture could be converted to the α,β -isomer by stirring with 0.1 M sodium methoxide in methyl alcohol under nitrogen at 0°C for 2 hr.

3. Discussion

Cyclohexenones with 2-alkyl substituents are usually prepared by alkylation of dihydroresorcinol followed by enol ether formation, reduction, and hydrolysis.^{2b} A variety of other approaches have been employed.² The procedure outlined here is simple, occurring in essentially one pot, using commercially available starting materials. The alkylating agent can equally well be an alkyl iodide or p -toluenesulfonate ester. A variety of other alkylating agents have been employed using an earlier, unoptimized version of this procedure.^{3,4}

1. Department of Pharmacology, School of Medicine, Vanderbilt University, Nashville, TN 37232.
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3. Taber, D. F. *J. Org. Chem.* **1976**, 41, 2649.
4. Note added in proof: Professor L. N. Mander has recently advised us that addition of 1.0 equivalent of potassium t -butoxide prior to addition of sodium metal significantly improved the yield of this procedure.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

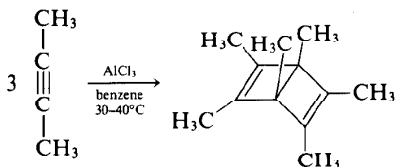
o -Anisic acid (8); Benzoic acid, 2-methoxy- (9); (579-75-9)

1-Bromoheptane: Heptane, 1-bromo- (8, 9); (629-04-9)

Cyclohexane-1,3-dione: 1,3-Cyclohexanedione (8, 9); (504-02-9)

HEXAMETHYL DEWAR BENZENE

(Bicyclo[2.2.0]hexa-2,5-diene, 1,2,3,4,5,6-hexamethyl-)



Submitted by SAMI A. SHAMA and CARL C. WAMSER¹

Checked by RETO NAEF, DIETER SEEBACH, and BEAT WEIDMANN

1. Procedure

Caution! See benzene warning, Org. Synth. **1978**, *58*, 168. This preparation should be conducted in an efficient hood and the operator should wear protective gloves.

A 250-mL, three-necked, round-bottomed flask containing a 2.5-cm magnetic stirring bar is equipped with a Dewar-type reflux condenser containing ice, a dropping funnel, and a gas inlet tube. A calcium chloride drying tube is attached to the condenser and the apparatus is flushed with dry deoxygenated nitrogen (Note 1). The gas inlet tube is then replaced by a thermometer, and a suspension of 5.0 g of aluminum trichloride in 50 mL of benzene is introduced into the flask (Note 2). A solution of 100 g (1.85 mol) of 2-butyne (Notes 3 and 4) in 50 mL of cold dry benzene is added, with vigorous stirring, through the dropping funnel, over a period of 1 hr. During the addition, the temperature of the reaction mixture is kept between 30 and 40°C through the use of a water bath. Stirring is continued for 5 hr at 30–40°C after the addition has been completed. The catalyst is then decomposed by pouring the mixture onto 50 g of crushed ice in a 500-mL separatory funnel, whereupon the dark brown color turns pale yellow. When the ice has melted completely, the organic layer is separated, washed with two 25-mL portions of cold water, dried over anhydrous potassium carbonate, and filtered. Benzene and unreacted butyne (Note 5) are removed in a rotary evaporator using a water bath at 40°C and a water aspirator vacuum. The residual liquid is

distilled through a short-path distillation head under reduced pressure using a capillary. The yield is 38–50 g (38–50%) of hexamethyl Dewar benzene, bp 43°C/10 mm, mp 7–8°C, n_D^{20} 1.4480 (Notes 6 and 7).

2. Notes

1. Commercial nitrogen is deoxygenated by bubbling it through a trap containing an alkaline pyrogallol solution.² The gas is then dried by passing it through a potassium hydroxide tower. The checkers used argon as an inert atmosphere.

2. Aluminum trichloride is purified by sublimation under reduced pressure and the benzene is dried over sodium wire before use. The checkers used sublimed $AlCl_3$ as supplied by Merck (Darmstadt).

3. 2-Butyne was purchased from Chemical Samples Company or from Fluka AG.

4. The bottle containing 2-butyne (bp 27°C) should be chilled thoroughly before opening.

5. About 20 g of 2-butyne may be collected in an ice-cooled receiver if the dried solution is concentrated by distillation through a 25-cm Vigreux column rather than by evaporation. The checkers do not recommend this mode of work-up, nor did they use a column for distilling the Dewar benzene, to avoid prolonged heating of the bicyclic system.

6. The spectral properties of hexamethyl Dewar benzene are as follows: 1H NMR ($CDCl_3$) δ : 1.07 (s, 6 H), 1.58 (s, 12 H).

7. Hexamethyl Dewar benzene undergoes thermal isomerization^{3,4} and reacts with acids⁵ and transition metal ions.⁶ It should be stored in a freezer in a tightly sealed bottle. Hexamethyl Dewar benzene is reportedly a carcinogen,⁷ and care must be taken to avoid contact with the skin or inhalation of its vapor.

3. Discussion

The present procedure is that of Schäfer^{8,9} and is the first method available for large-scale preparation of a Dewar benzene. Other syntheses of compounds containing the Dewar benzene skeleton have generally involved photochemical isomerization of the corresponding benzene isomer.¹⁰

The present procedure represents a novel reaction, bicyclotrimerization. The intermediate dimeric complex of AlCl_3 with tetramethylcyclobutadiene has been isolated, and addition of different alkynes to this complex provides a synthetic route to a variety of substituted Dewar benzenes.¹¹

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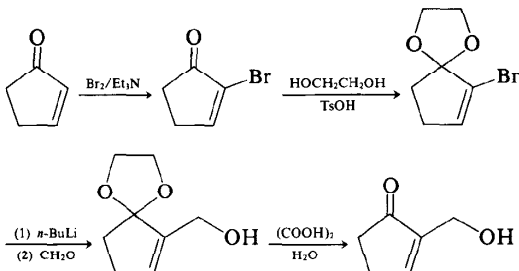
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Hexamethyl Dewar benzene: Bicyclo[2.2.0]hexa-2,5-diene, 1,2,3,4,5,6-hexamethyl- (8, 9); (7641-77-2)

2-Butyne (8, 9); (503-17-3)

2-HYDROXYMETHYL-2-CYCLOPENTENONE



Submitted by AMOS B. SMITH, III, STEPHEN J. BRANCA, MICHAEL A. GUACIARO, PETER M. WOVKULICH, and ABNER KORN¹

Checked by F. PIGOTT and G. SAUCY

1. Procedure

A. *2-Bromo-2-cyclopentenone*. In a well-ventilated hood, a solution of 18.98 g (231.2 mmol) of 2-cyclopentenone (Note 1) in 150 mL of carbon tetrachloride is added to a 1-L, three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer, and an addition funnel. The solution is chilled to 0°C with an ice bath and a solution of 40.5 g (253.4 mmol, 13.0 mL) of bromine in 150 mL of carbon tetrachloride is added dropwise during 1 hr. Then a solution of 35.1 g (346.8 mmol, 48.3 mL) of triethylamine in 150 mL of carbon tetrachloride is added dropwise over 1 hr with vigorous stirring while the reaction is held at 0°C. Stirring is continued for an additional 2 hr at room temperature; the resulting dark suspension is filtered with suction and the filter cake washed with carbon tetrachloride. The filtrate and washings are combined and washed with two 100-mL portions of 2 *N* hydrochloric acid, one 100-mL portion of saturated sodium bicarbonate solution, one 100-mL portion of water, and one 100-mL portion of saturated sodium chloride solution. The resultant solution is dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. Distillation of the resultant oil (69–78°C, 1.0 mm) afforded 23.7 g (147.2 mmol, 64%) (Note 2) of a white crystalline solid (mp 36–37°C, lit.² mp 39–39.5°C) (Note 3).

B. 2-Bromocyclopentenone ethylene ketal. A solution of 22.00 g (136.7 mmol) of freshly distilled 2-bromo-2-cyclopentenone, 21.80 g (351.2 mmol) of ethylene glycol, 1.5 L of benzene (Note 4), and 60 mg of *p*-toluenesulfonic acid monohydrate is refluxed for 64 hr (Note 5), with azeotropic removal of water, in a 3-L, round-bottomed flask, equipped with a Dean-Stark trap, condenser, and Drierite drying tube. The solution is cooled to room temperature, dried with potassium carbonate, and filtered by vacuum through 15 g of Celite. The filter cake is washed with 150 mL of benzene. Removal of the solvent under reduced pressure yields a mobile yellow oil. Distillation (65–67°C, 0.7 mm) affords 22.4 g (109.0 mmol, 80%) (Note 6) of the ketal (Note 7).

C. 2-Hydroxymethyl-2-cyclopentenone. The apparatus, as illustrated in Figure 1 (Note 8), is flame-dried while dry nitrogen is passed through. Paraformaldehyde (13 g, 433 mmol) (Note 9) is then added to the 250 mL flask (the generator) and 19.4 g (94.6 mmol) of freshly distilled 2-bromo-2-cyclopentenone ethylene ketal in 300 mL of dry tetrahydrofuran containing 2 mg of 2,2'-bipyridyl (Note 10) is added to the 500-mL flask (the reaction flask). The reaction flask is chilled to -78°C with an acetone/dry ice bath and 46.0 mL (105.8 mmol) of *n*-butyllithium (2.3 *M* in hexane) (Note 11) is added dropwise by syringe through the rubber septum during 1 hr. The resultant red solution is stirred for 1 hr and then warmed to -30°C using a methanol–water (2 : 3)/dry ice bath. An oil bath previously heated to 160°C is applied to the generator and the monomeric formaldehyde thus generated is bubbled into the reaction

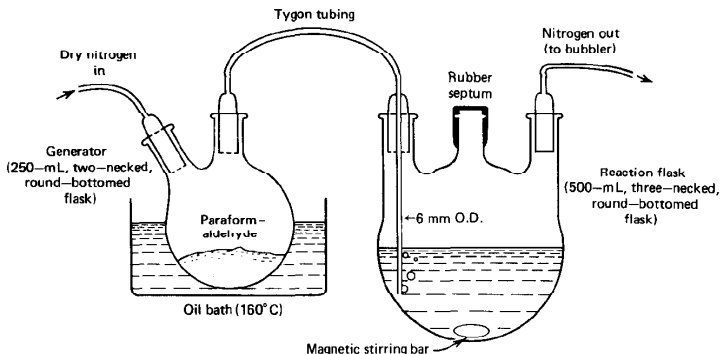


Figure 1

mixture via a steady stream of dry nitrogen until the red color of the indicator is discharged (approximately 45 min). The reaction is quenched by the addition of 10 mL of saturated ammonium chloride solution and the resultant mixture is poured into 100 mL of a saturated sodium chloride solution. This mixture is extracted four times with 100-mL portions of methylene chloride; the methylene chloride extracts are combined and dried over magnesium sulfate. After filtration, evaporation of the solvent under reduced pressure affords 8.1–10.7 g (Note 12) of crude 2-hydroxymethyl-2-cyclopentenone ethylene ketal as a viscous liquid (Note 13).

Without purification, 8.1 g of the above crude ketal is added to a solution consisting of 1.0 g of oxalic acid, 5 mL of water, and 40 mL of methylene chloride. The resultant mixture is stirred for 5 hr at room temperature. At the end of this period the solution is filtered through 50 g of magnesium sulfate impregnated with 1.0 g of potassium carbonate (Note 14). Evaporation of the solvent from the filtrate affords a solid which, after purification by short-path distillation (70–80°C, 0.1 mm) (Note 15), gives 4.9 g (46%, based on bromoketal) (Note 16) of pure 2-hydroxymethyl-2-cyclopentenone, mp 68–69°C (off-white crystals) (Notes 17 and 18).

2. Notes

1. Cyclopentenone is commercially available from the Aldrich Chemical Company, Inc., or may be prepared according to the procedure of DePuy; see *Org. Synth. Collect. Vol.* **1973**, V, 326.

2. The checkers obtained somewhat higher yields (i.e., 66 and 77%).

3. Pure 2-bromo-2-cyclopentenone obtained by recrystallization from diethyl ether–hexane (Ref. 2) displayed the following spectroscopic properties: IR (CCl_4) cm^{-1} : 1720 (s), 1595 (m); ^1H NMR (CCl_4 , 60 MHz) δ : 2.35–2.60 (m, 2 H), 2.60–2.91 (m, 2 H), 7.40 (t, 1 H, $J = 2$).

4. Benzene is a potential carcinogen!

5. The reaction progress was monitored by TLC analysis (silica gel) using hexane–ethyl acetate (4 : 1, v/v) with 3.5% methanolic phosphomolybdic acid as indicator: bromoketal, R_f 0.37, bromoketone, R_f 0.15.

6. The bromoketal appears to be somewhat unstable and should be used as soon as possible after preparation. Some decomposition was observed during distillation.

7. Pure 2-bromo-2-cyclopentenone ethylene ketal displayed the following spectroscopic properties: IR (CCl_4) cm^{-1} : 2975 (s), 2950 (s), 2880

(s), 1615 (w); ^1H NMR (CCl_4 , 60 MHz) δ : 1.95–2.55 (m, 4 H), 3.71–4.01 (m, 2 H), 4.01–4.33 (m, 2 H), 6.05 (t, 1 H, $J = 2$).

8. The checkers found that it is important to employ tubing of wide bore (6 mm O.D.) to conduct the gaseous formaldehyde from the generation flask into the reaction flask to avoid the possibility of the tube becoming plugged.

9. Prior to use paraformaldehyde was dried overnight in high vacuum (0.1 mm) over phosphorus pentoxide.

10. The reagent 2,2'-bipyridyl, available from the Aldrich Chemical Company, Inc., appears red in solutions containing organolithium and organomagnesium reagents³ and is thereby an excellent indicator. Its use here allows addition of the precise amount of gaseous formaldehyde.

11. *n*-Butyllithium is available commercially from Alfa Products, Ventron Corporation.

12. The checkers found this crude product to contain 84.5% of the desired ketal, based on GC analysis.

13. Although 2-hydroxymethyl-2-cyclopentenone ethylene ketal could be purified by Kugelrohr distillation (88–100°C, 0.10 mm) this was not necessary for successful completion of the subsequent hydrolysis step. Pure 2-hydroxymethyl-2-cyclopentenone ethylene ketal possesses the following spectroscopic properties: IR (CCl_4) cm^{-1} : 3470–3500 (s), 1616 (w); ^1H NMR (CCl_4 , 60 MHz) δ : 1.68–2.17 (m, 2 H), 2.17–2.58 (m, 2 H), 2.58–2.93 (br s, 1 H), 3.87 (s, 4 H), 3.98–4.16 (m, 2 H), 5.81–6.03 (m, 1 H).

14. The function of the potassium carbonate is to neutralize the oxalic acid as the solution passes through.

15. The short-path distillation of 2-hydroxymethyl-2-cyclopentenone is carried out without a water condenser. Furthermore, to prevent solidification of the distillate in the condenser, gentle warming of the condenser with a heat gun may be necessary.

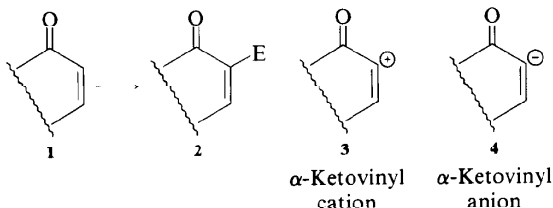
16. The submitters had obtained a 70% yield for this two-step sequence, the crucial step being the reaction with formaldehyde.

17. Pure 2-hydroxymethyl-2-cyclopentenone displayed the following spectroscopic properties: IR (CHCl_3) cm^{-1} : 3400–3450 (s), 1680 (s), 1630 (m); ^1H NMR (CDCl_3 , 60 MHz) δ : 2.27–2.84 (m, 4 H), 3.00 (br s, 1 H), 4.33 (d, 2 H, $J = 1$), 7.60 (m, 1 H).

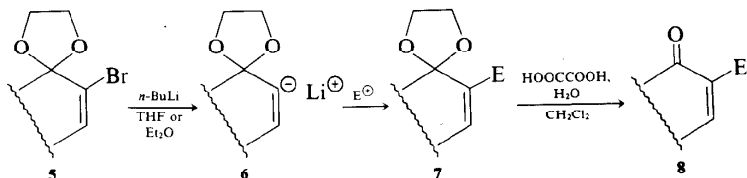
18. The overall yield from cyclopentenone to 2-hydroxymethyl-2-cyclopentenone over a number of runs was found to be in the range of 23–28%. The submitters had obtained 34.5%.

3. Discussion

The procedure reported here provides an efficient method for the construction of a wide variety of α,β -unsaturated ketones directly from the parent enone (i.e., **1** \rightarrow **2**), which does not require intervention of the thermodynamic dienolate. To our knowledge, a *general* solution for this recurring synthetic problem is unavailable, although Corey et al.,⁴ Fuchs,⁵ and Stork and Panaras⁶ have independently developed a reverse polarity (umpolung) strategy for α -arylation of α,β -unsaturated ketones. Central to their approach was the generation of an effective latent equivalent for α -ketovinyl cation **3**. Such a strategy, however, is limited in that it depends critically upon the availability of the requisite alkyl or aryl organocuprate or magnesium reagent.



A more versatile, as well as a more direct approach for the conversion of **1** to **2** employs the ethylene ketal of α -bromo- α,β -enones (e.g., **5**) as a latent equivalent of α -ketovinyl anion **4**.⁷ Indeed, independent studies by Ficini and Depeyaz,⁸ House and McDaniel,⁹ and Manning et al.¹⁰ as well as our own¹¹ suggested that such a general strategy would be viable. To illustrate this approach, we record here the preparation of the very useful synthon α -hydroxymethyl-2-cyclopentenone:



The overall efficiency of this sequence demonstrates, we believe, the considerable promise that α -bromoketals of α,β -enones hold as latent α -

ketovinyl anion equivalents. In particular, we note the feasibility of introducing the very useful trimethylsilyl, tri-*n*-butyltin, and phenylselenenyl substituents.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Bromo-2-cyclopentenone: 2-Cyclopenten-1-one, 2-bromo- (8); (10481-34-2)

2-Cyclopentenone: 2-Cyclopenten-1-one (8, 9); (930-30-3)

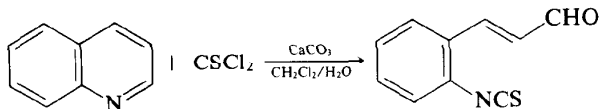
Ethylene glycol (8); 1,2-Ethanediol (9); (107-21-1)

Paraformaldehyde (9); (30525-89-4)

2,2'-Bipyridyl: 2,2'-Bipyridine (8, 9); (366-18-7)

***o*-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE**

(2-Propenal, 3-(2-isothiocyanatophenyl)-, (*E*)-)



Submitted by R. FARRAND and R. HULL¹

Checked by K. E. FAHRENHOLTZ and G. SAUCY

1. Procedure

Caution! This reaction should be carried out in a good hood.

A 1000-mL (Note 1), multinecked flask is provided with an efficient stirrer, vented outlet, thermometer, and 250-mL dropping funnel. The flask is surrounded by an ice/water bath and charged with 62.5 mL (68.4 g, 0.53 mol) of quinoline, 250 mL of dichloromethane, 55 g (0.55 mol) of finely powdered calcium carbonate, and 250 mL of water. The mixture is stirred vigorously, cooled to 10°C, and maintained at 10–15°C as a solution of 37.5 mL (56.5 g, 0.49 mol) of thiophosgene (Note 2) in 120 mL of dichloromethane is added over 15 min. There is very little exotherm or foaming. The cooling bath is removed and the reaction mixture is stirred vigorously at ambient temperature overnight. The reaction is then filtered through a bed of filter aid. The layers are separated and the aqueous layer is extracted with 50 mL of dichloromethane. The combined organic layers are washed twice with 150 mL of 2 *N* hydrochloric acid (Note 3), then with 150 mL of water, and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gives 95–103 g of crude material (Note 4). This is dissolved with heating in 400 mL of cyclohexane, decolorizing carbon is added, and the mixture is filtered through a bed of filter aid. The filtrate is heated under reflux for 2 hr (Note 5) and allowed to cool with stirring (Note 6). The resulting solid is isolated by filtration, washed with cyclohexane, and dried in a vacuum oven at 40°C to give 78–83 g (84–89%) of *o*-isothiocyanato-(*E*)-cinnamaldehyde as cream crystals, mp 77–79°C (Note 7).

2. Notes

1. The reaction has been carried out on 10 times these quantities with no difficulty.

2. The checkers used an older bottle of thiophosgene and obtained an 84% yield (based on thiophosgene). A subsequent run was carried out with Aldrich "85% in CCl_4 " thiophosgene found by analysis to contain 63% thiophosgene (therefore 89.4 g was used) and an 89% yield was obtained. A subsequent run on an *unanalyzed* bottle of the same lot number using 89.4 g gave a 100% yield (92% based on quinoline). It is suggested that thiophosgene be analyzed before use (Note 8).

3. These two washes remove unreacted quinoline.

4. The crude material consists of a mixture of *Z* and *E* isomers, with *Z* predominating. If work-up of the reaction is delayed, more of the less soluble *E* isomer is formed, complicating subsequent filtration.

5. This additional heating completes the isomerization of the *Z* to the *E* isomer.

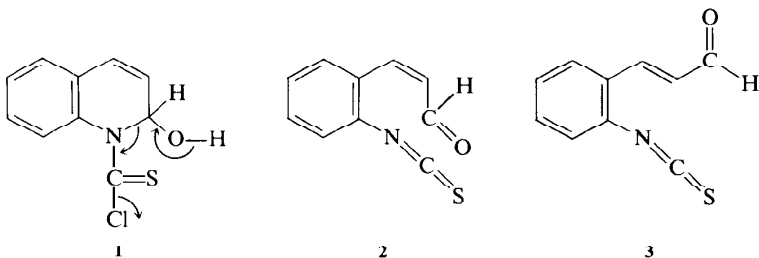
6. Subsequent breakup and filtration of the solid are facilitated if this solution is transferred and allowed to cool with stirring in a large-mouth container such as a beaker.

7. Melting points were taken in open capillaries on a Thomas-Hoover melting point apparatus. The crude material can be purified by dissolving it in dichloromethane, passing the solution over a plug of silica gel, and concentrating the solution with the addition of ether. The recrystallized material has essentially the same melting point and is colorless. The spectral properties of *o*-isothiocyanato-(*E*)-cinnamaldehyde are as follows: IR (Nujol) cm^{-1} : 2075 (NCS) and 1670 (conjugated C=O); ^1H NMR (CDCl_3) δ : 6.75 (d of d, 1 H, $J = 16$ and 7.5, CH=CHCHO), 7.4 (m, 4 H, aromatic H), 7.8 (d, 1 H, $J = 16$, ArCH=CH), 9.78 (d, 1 H, $J = 7.5$, CHO).

8. Thiophosgene mixed with CCl_4 can be analyzed as follows: a 0.5-mL aliquot of the reagent is mixed with a warm mixture of 15 mL of 30% hydrogen peroxide and 15 mL of 1 *N* sodium hydroxide. The mixture is shaken occasionally during 20 min (overnight gives the same titer) and diluted to 200 mL with water. Liberated Cl^- is then titrated with mercuric nitrate.

3. Discussion

This procedure is an example of a simple fission reaction of *N*-heterocyclic compounds by thiophosgene and base² wherein the dihydro intermediate **1** undergoes ring fission to yield the *Z*-isothiocyanate **2** which isomerizes *in situ* to the *E*-isomer **3**. The reaction may be applied to



certain substituted quinolines,^{3,4} isoquinoline,² pyridine,⁵ benzoxazole,⁶ benzimidazole,^{6,7} and oxazole⁸ derivatives, but not to benzothiazole.⁶

The ortho-substituted isothiocyanates are valuable intermediates for the preparation of a variety of heterocyclic compounds; for example, *o*-isothiocyanato-(*E*)-cinnamaldehyde with sodio diethyl malonate undergoes facile cyclization to 3-formylquinoline-2(1*H*)-thione,⁹ which in turn may be used for the preparation of tricyclic^{9,10} and large ring heterocyclic compounds.¹¹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

o-Isothiocyanato-(*E*)-cinnamaldehyde: Isothiocyanic acid, *o*-(2-formyl-vinyl)phenyl ester, (*E*)- (8); 2-Propenyl, 3-(2-isothiocyanatophenyl)-, (*E*)- (9); (19908-01-1)

Quinoline (8, 9); (91-22-5)

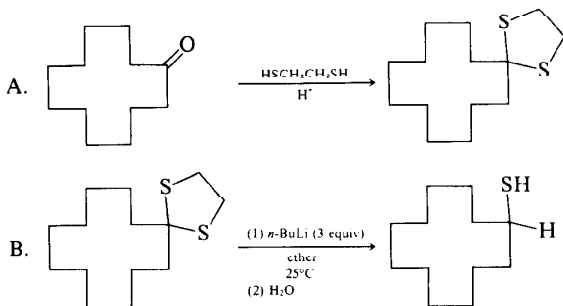
Thiophosgene (8); Carbonothioic dichloride (9); (463-71-8)

o-Isothiocyanato-(*Z*)-cinnamaldehyde: Isothiocyanic acid, *o*-(2-formyl-vinyl)phenyl ester, (*Z*)- (8); (19908-02-2)

Sodio diethyl malonate: Malonic acid, diethyl ester, ion(1-), sodium (8); Propanedioic acid, diethyl ester, ion(1-), sodium (9); (996-82-7)

3-Formylquinoline-2(1*H*)-thione: 3-Quinolinecarboxaldehyde, 1,2-dihydro-2-thioxo- (9); (51925-41-8)

MERCAPTANS FROM THIOKETALS: CYCLODODECYL MERCAPTAN



Submitted by S. R. WILSON¹ and G. M. GEORGIADIS¹
Checked by E. VEDEJS, P. C. CONRAD, and M. W. BECK

1. Procedure

Caution! This procedure should be carried out in an efficient hood to prevent exposure to alkane thiols or benzene.

A. *1,4-Dithiaspiro[4.11]hexadecane*. A mixture of 46.5 g (0.26 mol) of cyclododecanone (Note 1), 24.1 g (21.5 mL, 0.26 mol) of 1,2-ethanedithiol (Note 1), and 0.75 g (0.004 mol) of *p*-toluenesulfonic acid monohydrate (Note 2), in 200 mL of benzene (Note 3) is placed in a 500-mL, three-necked reaction flask equipped for reflux under a water separator.² The mixture is heated at reflux for several hours until the theoretical amount of water (0.26 mol = 4.6 mL) has collected in the Dean-Stark trap. The reaction mixture is cooled and transferred to a separatory funnel. The mixture is washed with water, the benzene is removed on a rotary evaporator, and the residue is placed under reduced pressure (<0.1 mm) for several hours to remove traces of solvent. Approximately 66 g (99%) of a white solid is recovered (0.26 mol, mp 84–86°C). The crude material is pure by GLC and TLC, and is used in the next step with no further purification.

B. *Cyclododecyl mercaptan*. In a 1-L, three necked, round-bottomed flask equipped with a mechanical stirrer and nitrogen inlet and outlet stopcocks are placed 25.8 g (0.10 mol) of 1,4-dithiaspiro[4.11]hexadecane and 300 mL of ether, freshly distilled from sodium. The mixture is purged with nitrogen, cooled to 0°C with an ice bath, and 125 mL (0.30 mol, 2.4 M in hexane) of butyllithium is added by syringe (Notes 4, 5) under a slow flow of nitrogen. The light yellow mixture is then allowed to warm to room temperature and stirred overnight with nitrogen stopcocks closed (Note 6). The reaction mixture is cooled to 0°C and 50 mL of water is added slowly and very carefully (Note 7). The resulting light brown solution is poured into 200 mL of water in a separatory funnel and, after shaking, the organic layer is separated. The solution is dried over MgSO₄, concentrated (aspirator), and distilled through a 10-cm Vigreux column at 103–108°C (1 mm) to give 17.2–17.9 g (86–90%) of pure cyclododecyl mercaptan (Notes 8, 9). A small forerun, bp < 95°C, (ca. 2 mL) is discarded.

2. Notes

1. The submitters used cyclododecanone and 1,2-ethanedithiol obtained from Aldrich Chemical Company, Inc.
2. The submitters used *p*-toluenesulfonic acid monohydrate from Matheson, Coleman, and Bell.
3. The checkers used toluene in place of benzene.

4. The submitters used butyllithium from Alfa Products, Ventron Corporation.

5. The reaction also occurs well with only 2 mol of butyllithium, but traces of starting material remain.

6. The reaction is complete in about 6 hr.

7. *Caution! Quenching of excess butyllithium is exothermic.*

8. By GLC analysis, the distilled cyclododecyl mercaptan is >95% pure. Sometimes the product is pale pink.

9. The distilled cyclododecyl mercaptan has the following spectral data: ^1H NMR (CCl_4) δ : 1.1 (d, 1 H, $J = 6$, S-H), 1.32 (broad s, 20 H), 1.64–1.82 (m, 2 H), 2.81 (m, 1 H, CHSH); IR (neat, μ) 3.4, 6.82, 6.94. Anal. Calcd for $\text{C}_{12}\text{H}_{24}\text{S}$: C, 71.93; H, 12.07; S, 16.00. Found: C, 71.83; H, 12.19; S, 16.03.

3. Discussion

Mercaptans are generally prepared by displacement reactions.³ However, secondary or hindered mercaptans are more difficult to obtain. The dithiolane cleavage reaction⁴ is a convenient "in situ" generation of thioketones which are known to be reduced⁵ with butyllithium to secondary mercaptans by β -hydrogen transfer. Table I shows a number of mercaptans prepared from *saturated* thioketals in 78–90% yields. The aryl example gives lower yields partly because of ring metalation.

TABLE I
MERCAPTANS FROM ETHYLENE THIOKETAL CLEAVAGE/REDUCTION

Ketone Thioketal	Bp/mp ($^{\circ}\text{C}$)	Yield (%)
Cyclododecanone	103–108 (1 mm)	90
4- <i>tert</i> -Butylcyclohexanone	~100 (0.5 mm)	90 ^a
2-Adamantanone	mp 139–142	79
4-Heptanone	127–135 (760)	81
Acetophenone	70–75 (0.5 mm)	36 ^a
Cyclohexanone	130–140 (760)	78 ^c
Estrone	mp 170–175	90 ^d
Pregnenolone	mp 108–113	65 ^d
Undecan-5-one	110–120 (0.3 mm)	93

^aAxial : equatorial ratio, 2 : 1.

^bBy extraction into KOH (purity = 85–93%).

^cDistillation could not cleanly separate thiol from octane (formed from the butyllithium).

^dMixture of isomers.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,4-Dithiaspiro[4.11]hexadecane (9); (16775-67-0)

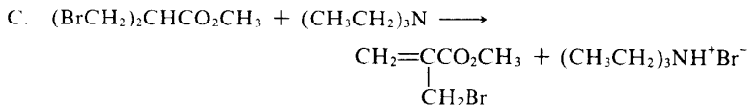
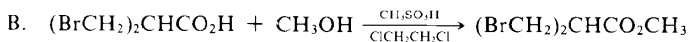
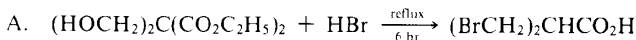
Cyclododecanone (8, 9); (830-13-7)

1,2-Ethanedithiol (8, 9); (540-63-6)

Butyllithium: Lithium, butyl- (8, 9); (109-72-8)

METHYL α -(BROMOMETHYL)ACRYLATE

(2-Propenoic acid, 2-(bromomethyl)-, methyl ester)



Submitted by JOHN M. CASSADY, GARY A. HOWIE, J. MICHAEL ROBINSON,
and IOANNIS K. STAMOS¹

Checked by PAUL R. WEST and ORVILLE L. CHAPMAN

1. Procedure

Caution! Methyl α -(bromomethyl)acrylate is a potent vesicant and lachrymator and should be handled with care. All operations should be carried out in an efficient hood in order to avoid contact.

A. *β,β' -Dibromoisobutyric acid.* To a 5-L, single-necked flask, equipped with a heating mantle, 22-cm Vigreux distillation head, thermometer, 30-cm water-cooled condenser with adapter, and 1-L, ice-cooled receiving vessel (Note 1) is added 440 g (2.0 mol) of diethyl bis(hydroxymethyl)malonate (Notes 2² and 3) and 3450 mL of concentrated aqueous hydrobromic acid (Note 4). Heating for 6 hr at vigorous reflux gives 2400 mL of aqueous distillate (Note 5). The undistilled concentrate is poured into a 3-L beaker, cooled overnight at -15°C (Note 6), and filtered through a 500-mL fritted-glass Büchner funnel using aspirator vacuum. After suction air drying for 6 hr, drying is continued for 6 days in a vacuum desiccator containing active Drierite and under 10 mm of initial vacuum (Note 7) to give 332 g (67.5%) of β,β' -dibromoisobutyric acid as a brown solid. Distillation of the filtrate to remove an additional 850 mL of aqueous hydrobromic acid (Note 8), followed by cooling and filtration, gives an additional 34.0 g (6.9%) of solid. Crude product, obtained in 74–85% yield (Note 9³), is suitable for use without further purification (Note 10).

B. *Methyl β,β' -dibromoisobutyrate.* In a 200-mL, round-bottomed flask fitted with a reflux condenser are placed 61.5 g (0.25 mol) of β,β' -dibromoisobutyric acid, 25 g (0.78 mol) of commercial methanol, 75 mL of ethylene dichloride, and 0.2 mL of methanesulfonic acid (Notes 11⁴ and 12). The reaction mixture is heated under reflux for 24 hr. The solution is cooled to room temperature, diluted with about 200 mL of methylene chloride, and neutralized with dilute, cold sodium bicarbonate solution (Note 13). The organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to remove most of the methylene chloride. Fractional distillation of this residue under reduced pressure (the receiver is cooled with an ice-salt mixture) yields 48.8 g (75%) of product, bp $64\text{--}65^{\circ}\text{C}$ (0.3 mm).^{3,5,6}

C. *Methyl α -(bromomethyl)acrylate.* In a dry, 250-mL three-necked flask, equipped with a mechanical stirrer, reflux condenser, and an addition funnel, 20 g (0.077 mol) of methyl β,β' -dibromoisobutyrate (Note 14^{5,6}) in 50 mL of anhydrous benzene (Note 15⁷) is stirred vigorously. Triethylamine (Notes 16⁸ and 17) (7.7 g, 0.076 mol) in 50 mL of benzene is introduced dropwise at a rate of about 3 mL per min. After the addition is complete the mixture is stirred for an additional 1 hr at room temperature, refluxed for 1 hr, and then cooled to 20°C . The reaction mixture is filtered with suction and the amine salt washed twice with 20 mL of benzene. The filtrate and washings are combined in a round-

bottomed flask and concentrated on a rotary evaporator at 30–35°C to remove most of the benzene. The residue is transferred to a small distillation apparatus and fractionally distilled at reduced pressure using an oil bath at 50–55°C. The yield of ester collected at bp 35–37°C (1.3 mm) is 11.0 g (80%) (Notes 18–21).

2. Notes

1. Cooling the receiving vessel greatly reduces loss of ethyl bromide.
2. Diethyl bis(hydroxymethyl)malonate was prepared up to an 8.0-mol scale by the method of Block.² After suction filtration to remove the drying agent, the dried diethyl ether extracts were concentrated directly on a Büchi rotary evaporator at aspirator vacuum using a bath temperature of 50°C; concentration was continued for ca. 2 hr after removal of the ether. The crude, oily diethyl bis(hydroxymethyl)malonate, obtained in 94–96% yield, solidified on standing and was suitable for use without further purification. The malonate can be stored at room temperature with no special precautions.

3. The checkers ran this reaction on a 20% scale [starting with 88 g (0.4 mol) of diethyl bis(hydroxymethyl)malonate]. At this scale, yields between 63 and 75% were realized.

4. Initial experiments used commercial 48% aqueous hydrobromic acid. In subsequent runs no decrease in yields was apparent when recovered distillate boiling at or above 110°C was substituted for the commercial acid.

5. Approximately 45 additional min of heating was required to reach distillation temperature. The first 780 mL (excluding ethyl bromide) of aqueous distillate boiled below 110°C and was discarded. The remaining distillate was recycled as described in Note 4.

6. Cooling in a refrigerator freezing compartment is satisfactory. The beaker should be sealed (e.g., using Saran Wrap) to prevent escape of corrosive fumes.

7. After the solid was dried in the desiccator, weight reductions of up to 10% were observed.

8. Special care must be used toward the end of the distillation to avoid overheating caused by removal of too much solvent. Overheating can result in an intractable gummy residue.

9. Failure to distill the maximum amount of concentrated hydro-

bromic acid, higher crystallization temperatures, and/or washing with water may account for the lower (66%) reported³ yield.

10. Storage at room temperature (under nitrogen or in a filled, sealed container) for periods in excess of 1 year resulted in no significant deterioration of the crude acid as judged by its suitability for use in step B. Preparation of acid was done on a 0.5 – to 3.4 – mol scale with no significant variation in yield.

11. These conditions are patterned after a general procedure for esterification reported by Clinton and Laskowski.⁴

12. The checkers ran this reaction on a 50% scale [starting with 30.75 g (0.125 mol) of β,β' -dibromoisobutyric acid] and obtained yields ranging from 66 to 67%.

13. A brown, emulsified layer, which separates on long standing, is formed between the organic and aqueous layers. This layer can also be taken up with an additional 200 mL of methylene chloride and dried with a sufficient amount of anhydrous sodium sulfate to recover the organic layer.

14. It is recommended that methyl β,β' -dibromoisobutyrate^{5,6} which has been purified by fractional distillation be used, since the presence of acidic compounds reduces the yield and the presence of any hydroxyl function gives a product mixture that cannot be purified by simple distillation.

15. The preparation of anhydrous benzene has been described.⁷

16. Commercial triethylamine is conveniently purified by two distillations from a 2% solution of phenyl isocyanate.⁸

17. In a parallel experiment, ethyldiisopropylamine (9.82 g, purified as in Note 16) was mixed with a solution of 20 g of methyl β,β' -dibromoisobutyrate in 100 mL of dry benzene. The reaction mixture was stored at room temperature for 10 hr and gently refluxed for 1 hr under nitrogen in the dark. After work-up and distillation the yield of the product was 80%.

18. Distillation at higher temperatures results in viscous residues with considerably reduced yields of the product. The receiver should be immersed in an acetone–dry ice bath in order to prevent loss of the product to the trap of the vacuum line.

19. The product is stable for long periods of time if kept under an inert atmosphere in the absence of light and in the refrigerator.

20. Ethyl α -(bromomethyl)acrylate is prepared similarly, bp 38–42°C (0.8 mm).

21. The checkers obtained a 76% yield.

3. Discussion

Although methyl and ethyl α -(bromomethyl)acrylate are used extensively as synthetic intermediates in the preparation of a variety of organic compounds,⁹⁻¹⁶ many of biological importance, they are not commercially available and their preparation in good yield on a large scale is therefore of interest. The procedures outlined above represent useful modifications of published literature routes to these compounds.

The procedure for the elimination of HBr from the dibromo ester is a modification of the method of Lawton and co-workers for *sui generis* generation of the methyl^{5,9} or ethyl ester¹⁰ during a reaction. Methyl α -(bromomethyl)acrylate has also been prepared by bromination of methyl methacrylate in 700°C steam¹⁷ and by dehydrohalogenation with sodium acetate in acetic acid.⁶ Ethyl α -(bromomethyl)acrylate has been prepared by dehydrohalogenation with the monosodium salt of ethylene glycol^{3,18} and ethyl diisopropylamine.¹¹ The latter reaction was reported by Öhler et al. with no experimental details for the elimination reaction. The use of triethylamine as reported in this procedure appears to be the most efficient and convenient method for dehydrobromination to these acrylate esters.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl α -(bromomethyl)acrylate: Acrylic acid, 2-(bromomethyl)-, methyl ester (8); 2-Propenoic acid, 2-(bromomethyl)-, methyl ester (9); (4224-69-5)

β,β' -Dibromoisobutyric acid: Propanoic acid, 3-bromo-2-(bromomethyl)- (9); (41459-42-1)

Diethyl bis(hydroxymethyl)malonate: Malonic acid, bis(hydroxymethyl), diethyl ester (8); (20605-01-0)

Methyl β,β' -dibromoisobutyrate: Propionic acid, 3-bromo-2-(bromomethyl)-, methyl ester (8, 9); (22262-60-8)

Triethylamine (8); Ethanamine, *N,N*-diethyl- (9); (121-44-8)

2-METHYL-3-PHENYLPROPANAL

(Benzenepropanal, α -methyl-)



Submitted by S. A. BUNTIN and R. F. HECK¹
Checked by C. M. TICE and C. H. HEATHCOCK

1. Procedure

A 250-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser, is charged with 0.49 g (2.2 mmol) of palladium acetate (Note 1), 20.4 g (100 mmol) of iodobenzene, 9.0 g (125 mmol) of 2-methyl-2-propen-1-ol, 12.6 g (125 mmol) of triethylamine, and 32.5 mL of acetonitrile (Note 2). The reaction vessel is placed in an oil bath at 100°C and the solution is heated to reflux for 11 hr under a nitrogen atmosphere. The reaction mixture is allowed to cool to room temperature and transferred to a 500-mL separatory funnel with the aid of 100 mL of ether and 100 mL of water. The organic layer is washed five times with 100 mL portions of water. The combined aqueous

layers are reextracted with 100 mL of ether. The organic layers are combined, dried over anhydrous sodium carbonate, and filtered. The organic layer is concentrated and distilled under reduced pressure. The product, 2-methyl-3-phenylpropanal, 12.05 g (82%), has a boiling range of 52–58°C at 0.40 mm (Note 3).

2. Notes

1. Palladium acetate was prepared by the method of Stephenson et al.² A suitable material is also available from the Strem Chemical Company or Alfa Inorganics.

2. Iodobenzene, 2-methyl-2-propen-1-ol, and triethylamine were obtained from the Aldrich Chemical Company, Inc. Acetonitrile was obtained from the J. T. Baker Chemical Company. All these reagents were used as received.

3. The 2-methyl-3-phenylpropanal is 90% pure by GLC. The product mixture contains 6% of another isomer, 2-methyl-2-phenylpropanal, and a small amount of 2-phenyl-2-propen-1-ol. A completely pure sample of the aldehyde is readily obtained by stirring the crude aldehyde with excess saturated aqueous sodium bisulfite solution for several hours, filtering the solid bisulfite adduct, washing with ether, and liberating the aldehyde with excess aqueous sodium bicarbonate. Redistillation gives the completely pure aldehyde in about 60% yield.

3. Discussion

The reaction of allylic alcohols and aryl halides in the presence of a palladium catalyst has been used in the past to prepare various β -arylaldehydes. The procedure described here is essentially that of Heck and Melpolder.³ A similar reaction has been carried out with bromobenzene and 2-methyl-2-propen-1-ol in hexamethylphosphoric triamide (HMPT) as solvent with sodium bicarbonate as base. A variety of other bases have also been used.⁴ 2-Methyl-3-phenylpropanal has been prepared by reacting palladium acetate and phenylmercuric acetate with 2-methyl-2-propen-1-ol.⁵

The aldehyde is also obtained by the hydroformylation of allylbenzene.⁶ An alternative method involves benzylation of 2-ethylthiazoline followed by reduction with aluminum amalgam and cleavage with mercuric chloride.⁷ A sixth method of preparation is the phenylation of 2-vinyl-5,6-

dihydro-1,3-oxazine with phenylmagnesium bromide followed by methylation and hydrolysis.⁸ Finally, arylation of 2-methyl-2-propen-1-ol with phenyldiazonium salts catalyzed by zero-valent palladium complexes give the title aldehyde.⁹

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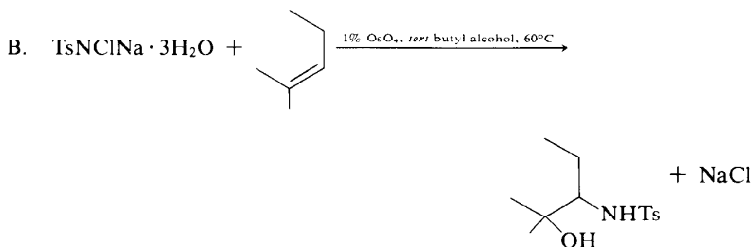
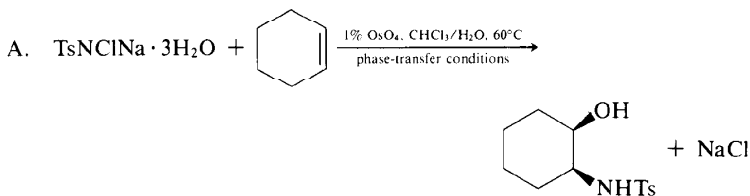
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Methyl-3-phenylpropanal: Hydrocinnamaldehyde, α -methyl- (8); Benzenepropanal, α -methyl- (9); (5445-77-2)
 Palladium acetate: Acetic acid, palladium(2+) salt (8, 9); (3375-31-3)
 Iodobenzene: Benzene, iodo- (8, 9); (591-50-4)
 2-Methyl-2-propen-1-ol: 2-Propen-1-ol, 2-methyl- (8, 9); (513-42-8)
 Phenylmercuric acetate: Mercury, (aceto)phenyl- (8); Mercury, (aceto-O)phenyl- (9); (62-38-4)

**OSMIUM-CATALYZED VICINAL OXYAMINATION
OF OLEFINS BY CHLORAMINE-T:
cis-2-(*p*-TOLUENESULFONAMIDO)CYCLOHEXANOL
AND 2-METHYL-3-(*p*-TOLUENESULFONAMIDO)-
2-PENTANOL**

[Benzenesulfonamide, *N*-(2-hydroxycyclohexyl)-4-methyl-, *cis*-]



Submitted by EUGENIO HERRANZ and K. BARRY SHARPLESS¹
Checked by RITA LOCHER, THOMAS WELLER, and DIETER SEEBACH

Caution! Because of the volatility and toxic nature of OsO₄, these reactions should be carried out in a well ventilated hood.

1. Procedure

A. *cis*-2-*p*-(Toluenesulfonamido)cyclohexanol. A 1-L, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.2 g (0.1 mol) of cyclohexene (Note 1), 250 mL of reagent grade chloroform (Note

2), and 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3). To the resulting black solution is added a solution of 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4) and 1.1 g (5 mmol) of benzyltriethylammonium chloride (Note 5) in 250 mL of distilled water. Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After 10 hr at 55–60°C, 14.2 g (0.1 mol) of sodium sulfite (Note 6) is added and the mixture is refluxed for 3 hr. The hot reaction mixture (Note 7) is transferred to a 1-L separatory funnel and allowed to stand for 10 min. The organic layer is collected in a 500-mL, round-bottomed flask. The aqueous layer is extracted once with 25 mL of CHCl_3 which is then combined with the original organic layer. Removal of solvent with a rotary evaporator provides a residue (Note 8) that is transferred to a 350-mL fritted-glass funnel and triturated successively with 200 mL and 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 9) and finally with two 50-mL portions of distilled water.

The resulting solid is placed in a 500-mL Erlenmeyer flask and dissolved in a mixture of 250 mL of CHCl_3 and 25 mL of CH_3OH . Anhydrous magnesium sulfate (ca. 8–10 g) is added and the resulting suspension is stirred magnetically for 5 min. Filtration of this suspension through a Celite mat on a sintered-glass funnel (Note 10), followed by evaporation of the solvent, affords (after drying under reduced pressure) 20.3–22 g (75–81.2%) of almost pure *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 155–157°C (Note 11). The oxyaminated product may be purified further by washing with toluene to give 20–21.8 g (74.3–80.9%); mp 157–158°C (Note 12).

B. 2-Methyl-3-(*p*-toluenesulfonamido)-2-pentanol. A 500-mL, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.4 g (0.1 mol) of 2-methyl-2-pentene (Note 1), 100 mL of reagent grade *tert*-butyl alcohol (Note 2), 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3), and 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4). Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After ca. 20 hr at 55–60°C, the mixture is cooled to room temperature using a water bath, and then 1.1 g (0.03 mol) of sodium borohydride is

added (Note 6). Stirring is continued at room temperature for about 1 hr. Removal of the solvent on a rotary evaporator gives an oil which is taken up in 100 mL of ethyl acetate and washed once with a solution that is prepared by mixing 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 13) with 25 mL of distilled water. The organic layer is washed twice more with 200 mL of saturated sodium chloride solution containing 1% sodium hydroxide and finally with 100 mL of saturated sodium chloride solution (Notes 9 and 14). Addition of anhydrous magnesium sulfate, filtration through a column of 75 g of silica gel (Note 15), elution with ethyl acetate (Note 16), and evaporation of the solvent on a rotary evaporator provides 21.5 g of the crude oxyaminated product (Note 17). The solid is then washed twice with ether (Note 18) to give 13.8–14.9 g (51–55%) of white, crystalline 2-methyl-3-(*p*-toluenesulfonamido)-2-pentanol, mp 96–97°C. Concentration of the ether yields an additional 4.0–5.0 g (15–18%) of oxyaminated product, mp 95–97°C (Note 19).

2. Notes

1. Cyclohexene and 2-methyl-2-pentene were used as commercially available.

2. The amount of solvent used is not critical. Several experiments have been performed at higher and lower concentrations and in all cases the yields were very much alike.

3. Osmium tetroxide was supplied commercially in 1-g amounts in sealed glass ampuls. The procedure we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide. The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO_4 . Each milliliter of this stock solution contains 25 mg (ca. 0.1 mmol) of OsO_4 . These solutions are stored in the hood at room temperature and seem to be very stable. We have also prepared five times more dilute solutions of OsO_4 in *tert*-butyl alcohol which we use in the case of small scale experiments.²

4. Chloramine-T trihydrate (CT) was obtained commercially. Excess chloramine-T is used because we have observed traces of the α -ketosulfonamide in those cases where the oxyaminated product contains a secondary hydroxyl group. We have also observed that these α -ketosulfonamides are further oxidized under the reaction conditions in a process which consumes several moles of chloramine-T.

5. Benzyltriethylammonium chloride was used as purchased.

6. The rates of reduction of the osmate esters vary considerably. We found that although the sulfite method (in the past we have also used sodium bisulfite) would reduce osmate esters from monosubstituted and 1,2-disubstituted olefins, however, osmate esters derived from trisubstituted and 1,1-disubstituted olefins were more inert to this treatment. Sodium borohydride reduces even these more hindered osmate esters rapidly at room temperature.

7. The oxyaminated product derived from cyclohexene is highly crystalline and begins to crystallize if the chloroform phase is allowed to cool.

8. The residue is dried under reduced pressure to remove the last traces of chloroform and *tert*-butyl alcohol, and then pulverized with a mortar and pestle.

9. In this way the *p*-toluenesulfonamide by-product along with some other impurities are removed from the oxyaminated product.

10. This treatment removes the suspended osmium particles from the solution.

11. GLC analysis revealed a purity of 99%.

12. The product obtained by this procedure is pure enough for most purposes. Its melt, however, is faintly cloudy. A product of higher purity, giving a clear melt, mp 158–159°C, can be obtained by recrystallization from about 10 mL of CHCl_3 per gram of oxyaminated product. The structural characterization of *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 158–159°C, is as follows. Anal. Calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{S}$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.81; H, 6.98; N, 5.19. ^1H NMR (CDCl_3) δ : 1.2–1.9 (m, 8 H, CH), 2.26 (d, 1 H, $J = 4$, OH), 2.44 (s, 3 H, Ar CH_3), 3.30 (m, 1 H, NCH), 3.80 (m, 1 H, OCH), 5.30 (d, 1 H, $J = 7$, NH), 7.55 (AA'BB' pattern, 4 H, $J = 8$, ArH); IR (KBr pellet) cm^{-1} : 3420, 3150, 1305, 1285, 1145, 1085, 550 all (s); 2920, 2850, 1440, 970, 930, 890, 815, 660 all (m); 1590, 1370, 1250, 1195, 1185, 1060,

1000 all (w). GC analysis was carried out using the following conditions: 6-ft \times 2-mm glass column, packed with 5% OV-17 on 80/100 Gas-Chrom Q, at 70 \rightarrow 250°C (32°C/min), retention time 9.50–9.60 min.

13. First a 1% solution of NaOH is prepared and then sodium chloride is added until saturation is reached. For the first washing, 25 mL of distilled water is added to 100 mL of the above solution in order to dissolve the inorganic salts present in the reaction mixture.

14. When ethyl acetate is used as the extracting solvent, rapid separation of the two phases was achieved. If a slight emulsion forms at the interphase during the last wash, the addition of celite and subsequent filtration improves the separation.

15. Silica Gel 60 (70–230 mesh ASTM) was used as obtained commercially. A column 50 cm long by 3.5 cm in diameter was used.

16. Approximately 700 mL of EtOAc was necessary to elute all the oxyaminated product from the silica gel column (monitoring by TLC elution with EtOAc is continued until a UV active spot does not appear on TLC). To speed up filtration a slight pressure of 4 psi is applied.

17. The product is a yellowish-brown solid that usually crystallizes when the last traces of EtOAc are removed on the rotary evaporator. If problems are encountered in inducing crystallization, either high vacuum or addition of ether followed by concentration should yield the desired solid.

18. The solid was washed in a 60-mL, sintered-glass funnel, the first time with 30 mL of ether and the second time with 25 mL.

19. The product obtained by this procedure is relatively pure. However, a product of higher purity, giving a clear melt, mp 99–100°C, can be obtained by recrystallization from about 1 mL of toluene per gram of oxyaminated product.

3. Discussion

This osmium-catalyzed procedure provides the first practical and direct means for the *cis* addition of a hydroxyl group and an arylsulfonamido moiety (ArSO_2NH) to an olefinic bond. The resulting vicinal hydroxy arylsulfonamides may in some cases be useful in their own right, but they are easily transformed in a variety of selective and potentially useful

Procedure A is very effective for most monosubstituted and 1,2-disubstituted olefins. This method,² using phase-transfer conditions (PTC), has been developed recently in our laboratory and represents a substantial improvement over our former procedures.⁴ Cyclooctene, (Z)-5-decene, stilbene, ethyl crotonate, and 1-decene are among the olefins that are readily oxyaminated under the conditions described in procedure A.

It is important to point out that the work-up we have used in the case of cyclohexene is a peculiar one because of the exceptional crystallinity of the oxyamination product. Generally, removal of the *p*-toluenesulfonamide is accomplished by shaking the chloroform layer with a saturated sodium chloride solution containing 1% sodium hydroxide.

The chloramine derivatives ($\text{ArSO}_2\text{NCINa}$) of a variety of other arylsulfonamides (Ar = phenyl, *o*-tolyl, *p*-chlorophenyl, *p*-nitrophenyl, and *o*-carboalkoxyphenyl) have been used successfully in these catalytic oxyaminations. Since only chloramine-T (Ar = *p*-tolyl) and chloramine-B (Ar = phenyl) are commercially available, we have developed a convenient procedure for generating the chloramines *in situ* for use in the modification involving phase-transfer catalysis. One simply stirs a suspension of the arylsulfonamide with an equivalent of sodium hypochlorite (Clorox) until a homogeneous solution is obtained. When this solution is used in the PTC method (see Ref. 2 for experimental details), the yields of oxyaminated product are comparable with those obtained with isolated chloramine salts.

The PTC method gives poor results with trisubstituted and 1,1-disubstituted olefins. The oxyamination product may still form, but it is accompanied by a number of by-products. Fortunately, this class of olefins is successfully oxyaminated by the alternative procedure (B). Methylcyclohexene, α -methylstyrene, 2-methyl-2-hepten-6-one, and its ketal are examples of olefins that give oxyamination products in good yield following procedure B.

Addition of a phase-transfer catalyst such as dicyclohexyl-18-crown-6 to the reaction mixture (in procedure B) results in a faster reaction rate. However, there are no significant changes in the final yield of oxyamination product.

We have carried out experiments on a 1-mol scale in the case of cyclohexene and α -methylstyrene (in the cyclohexene 1-mol experiment, the reaction mixture was 2.5 times more concentrated than described here), and have realized 70–80% and 65–75% yields, respectively, of the oxyaminated products.

Procedure A does not succeed with diethyl fumarate and 2-cyclohexen-1-one. Both chloramine T and part of the olefin are consumed, but the oxyamination product has not been detected in the reaction mixtures. It seems likely that it forms, but is unstable to the reaction conditions. Both of these olefins do form isolable oxyamination products under the milder conditions (room temperature) of a more recent oxyamination procedure.⁵

Procedure B does not succeed with tetramethylethylene and cholesterol and it seems reasonable to anticipate negative results with most hindered tri- and tetrasubstituted olefins. No reaction occurs, and chloramine-T is not consumed.

The sulfonamide protecting group on the nitrogen may be undesirable in some cases. For this reason we have developed an analogous osmium-catalyzed procedure which effects *cis* addition of hydroxyl and carbamate (ROCONH) moieties across the olefinic linkage.⁵ β -Amino alcohols with benzyloxycarbonyl (*Z* or CBZ) and *tert*-butoxycarbonyl (BOC) protecting groups on the nitrogen are accessible directly from the corresponding olefins by the new method.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Chloramine T trihydrate: *p* Toluenesulfonamide, *N* chloro, sodium salt (8); Benzenesulfonamide, *N*-chloro-4-methyl-, sodium salt, trihydrate (9); (7080-50-4)

cis-2-(*p*-Toluenesulfonamido)cyclohexanol: Benzenesulfonamide, *N*-(2-hydroxy-cyclohexyl)-4-methyl-, *cis*- (9); (58107-40-7)

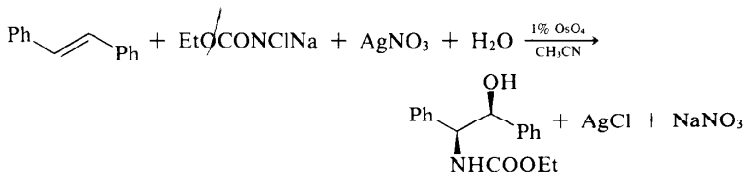
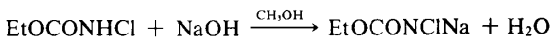
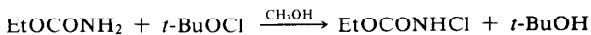
Cyclohexene (8, 9); (110-83-8)

Benzyltriethylammonium chloride: Ammonium, benzyltriethyl-, chloride (8); Benzenemethanaminium, *N,N,N*-triethyl-, chloride (9); (56-37-1)

2-Methyl-2-pentene: 2-Pentene, 2-methyl- (8, 9); (625-27-4)
tert-Butyl alcohol (8); 2-Propanol, 2-methyl-, (9); (75-65-0)
 Osmium tetroxide: Osmium oxide (8); Osmium oxide, (*T*-4)- (9); (20816-12-0)
 Sodium borohydride: Borate(1-), tetrahydro-, sodium (8, 9); (16940-66-2)
 Cyclooctene (8, 9); (931-88-4)
 (*Z*)-5-Decene: 5-Decene, (*Z*)- (8, 9); (7433-78-5)
 Stilbene: Stilbene, (*E*)- (8); Benzene, 1,1'-(1,2-ethenediyl)bis-, (*E*)- (9); (103-30-0)
 Ethyl crotonate: Crotonic acid, ethyl ester, (*E*)- (8); 2-Butenoic acid, ethyl ester, (*E*)- (9); (623-70-1)
 1-Decene (8, 9); (872-05-9)

**OSMIUM-CATALYZED VICINAL OXYAMINATION
 OF OLEFINS BY *N*-CHLORO-*N*-ARGENTOCARBAMATES:
 ETHYL *threo*-[1-(2-HYDROXY-1,2-DIPHENYL-
 ETHYL)]CARBAMATE**

[Carbamic acid (2-hydroxy-1,2-diphenylethyl)-, ethyl ester, (*R***R**)-]



Submitted by EUGENIO HERRANZ and K. BARRY SHARPLESS¹
 Checked by STEVEN D. YOUNG and CLAYTON H. HEATHCOCK

1. Procedure

A 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and a 100-mL addition funnel. The flask is placed in an ice

bath and charged with 13.36 g (0.15 mol) of ethyl carbamate (Note 1) and 100 mL of reagent grade methanol. Vigorous stirring is begun and to the ice-cold solution is carefully added 16.9 mL (16.2 g, 0.15 mol) of *tert*-butyl hypochlorite (Note 2). Fifteen minutes after the addition of the *tert*-butyl hypochlorite is complete, a methanolic solution (75 mL) of sodium hydroxide (6.43 g, 0.158 mol) is added dropwise over a period of several minutes (Note 3). After addition of the sodium hydroxide is complete, the ice bath is removed and stirring is continued for a further 10 min. The solvent is removed using a rotary evaporator (bath $<60^{\circ}\text{C}$) to give the crude ethyl *N*-chloro-*N*-sodiocarbamate as a white solid (Note 4). Addition of 400 mL of reagent grade acetonitrile and 26.33 g (0.1 mol) of silver nitrate (Note 5) results in the gradual appearance of a brown suspension. The solution is stirred for 5 min at room temperature; 18.23 g (0.1 mol) of (*E*)-stilbene (Note 6), 10 mL (~ 1.0 mmol) of a solution of OsO_4 in *tert*-butyl alcohol (Note 7), and 8.1 mL (0.45 mol) of water are then added. The milky brown suspension that results is stirred for 18 hr at room temperature. Filtration of the reaction mixture through a Celite mat on a sintered-glass funnel gives a yellow-brown solution (Note 8). The filtrate is refluxed for 3 hr with 200 mL of 5% aqueous sodium sulfite (Note 9). The resulting mixture is concentrated at aspirator pressure using a rotary evaporator until acetonitrile no longer distills. The residue, which is primarily aqueous, is extracted with two 60 mL portions of methylene chloride (Note 10). The organic phase is dried (MgSO_4) and concentrated to give 24.6 g of crude product as a pale yellow solid. Crystallization from 50 mL of hot toluene affords 18.6–19.8 g (66–69%) of almost pure ethyl *threo*-1-(2-hydroxy-1,2-diphenylethyl)carbamate, mp $120\text{--}122^{\circ}\text{C}$ (Note 11). Concentration of the mother liquors yields an additional 0.6–0.8 g of the hydroxy carbamate (Note 12).

2. Notes

1. Ethyl carbamate was obtained from the Aldrich Chemical Company, Inc.

2. *tert*-Butyl hypochlorite was obtained from Frinton Laboratories.

3. A 5% excess of sodium hydroxide was used to make sure that the *N*-chloro-*N*-sodiocarbamate was in a basic environment. The sodium hydroxide was obtained from J. T. Baker Chemical Company; it was 97.9% pure.

4. To remove the last traces of methanol the crude *N*-chloro-*N*-sodiocarbamate is placed under high vacuum (0.1 mm) for 15 min. Slightly higher yields of final product are obtained if the crude *N*-chloro-*N*-sodiocarbamate is purified by trituration with ether.

5. Silver nitrate was obtained from Apache Chemicals Inc.

6. (*E*)-Stilbene was used as obtained from Aldrich Chemical Company. The olefin should be added in small portions to avoid overheating of the reaction mixture.

7. Osmium tetroxide was supplied by Matthey-Bishop, Inc. in 1-g amounts in sealed glass ampuls. The procedure that we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean, brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide (Aldrich). The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO_4 . These solutions are stored in the hood at room temperature and seem to be very stable.

8. In this way the silver salts (AgCl) are removed from the reaction mixture. The precipitate is washed twice with 20-mL portions of acetonitrile.

9. The purpose of this sulfite treatment is to reduce and thereby remove the small amount of osmium that is bound to the organic products.

10. If an emulsion forms, addition of Celite and subsequent filtration through a sintered-glass funnel gives a clear separation of the two phases. The checkers found that extraction with three 100-mL portions of methylene chloride avoids emulsion formation.

11. Crystallization occurs at room temperature over a period of ca. 12 hr. The crystals are washed once with 15 mL of toluene or 50 mL of petroleum ether (bp 40–60°C). The product is quite pure. A product of higher purity, however, mp 122–123.5°C, can be obtained by a second crystallization from toluene.

12. After 24 hr at high vacuum (0.1 mm), some crystals appear. Addition of 15 mL of ether, filtration, and washing with 10 mL of ether give more product, mp 110–121°C. The checkers found that a higher overall yield was obtained if the mother liquors from the first recrystallization were dissolved in 50 mL of boiling diethyl ether. The solution is then brought to cloudiness by addition of petroleum ether (bp 40–

60°C). When this mixture is stored at 0°C overnight, brown crystals are deposited. Recrystallization of this material from 10 mL of hot toluene provides an additional 2.25–3.51 g of hydroxy carbamate, mp 114–117°C.

3. Discussion

This new procedure² for vicinal, *cis* addition of an oxygen and a nitrogen to an olefinic bond constitutes a major improvement over earlier methods,^{3,4} since the nitrogen is introduced bearing an easily removed protecting group. Although the procedure described here employs ethyl carbamate, both *tert*-butyl carbamate and benzyl carbamate can also be used. In fact, in most cases, higher yields are realized in oxyaminations using the latter carbamates.

N-Chloro-*N*-argentocarbamates are generated *in situ* by reaction of the corresponding *N*-chlorosodiocarbamates with silver nitrate in acetonitrile. The *N*-chlorosodiocarbamates are prepared from the carbamates according to the method of Campbell and Johnson.³ There are conflicting statements in the literature about the stability of these *N*-chlorosodiocarbamates.⁶ On one occasion, when EtOCONNaCl was prepared by the submitters on a 250-mmol scale, it decomposed rapidly (but not explosively), turning dark and releasing heat and gases. However, this same chloramine salt has been prepared on a 100-mmol scale without incident. The submitters have found that acidic conditions (which lead to contamination by the *N*-chlorocarbamate) are responsible for the spontaneous decomposition of these salts at room temperature. A simple modification of Campbell's procedure for preparing *N*-chloro-*N*-sodiocarbamates avoids this problem. By adding 5% more sodium hydroxide than the calculated amount, it is assured that all the *N*-chlorocarbamate in the reaction mixture is neutralized. No spontaneous decomposition has occurred in the batches of *N*-chloro-*N*-sodiocarbamates prepared in this way.

The regioselectivity of this new procedure toward terminal olefins is considerably better than that realized with the earlier catalytic oxyamination procedures based on chloramine-T.³ However, the catalytic procedure cannot compete with the regiospecificity exhibited by the stoichiometric *tert*-alkyl imido osmium reagents.³

This new catalytic procedure shows a different range of reactivity when compared with the chloramine-T based procedures, being very effective for mono- and 1,2-disubstituted olefins, especially electron-deficient ole-

fins such as dimethyl fumarate and (*E*)-stilbene. However, when the steric hindrance of the olefin increases (trisubstituted olefins), the oxyamination reaction proceeds slowly and affords mixtures of products. Very recently we have been able to oxyaminate trisubstituted olefins (2-methyl-2-heptene, 1-methylcyclohexene, 1-phenylcyclohexene, 3-methyl-2-cyclohexenone) using other *N*-chloro-*N*-metallocarbamates in conjunction with the addition of tetraethylammonium acetate (Et₄ NOAc).⁷

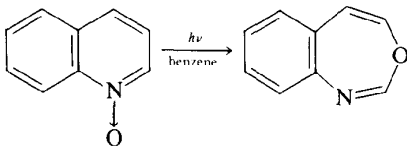
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl *threo*-[1-(2-hydroxy-1,2-diphenyl)ethyl]carbamate: Carbamic acid (2-hydroxy-1,2-diphenylethyl)-, ethyl ester, (*R**,*R**)- (9); (73197-89-4)
Ethyl carbamate: Carbamic acid, ethyl ester (8, 9); (51-79-6)
Ethyl *N*-chloro-*N*-sodiocarbamate: Carbamic acid chloro-, ethyl ester, sodium salt; (8, 9); (17510-52-0)
(*E*)-Stilbene (8); Benzene, 1,1'-(1,2-ethenediyl)bis-, (*E*)- (9); (103-30-0)

**1,3-OXAZEPINES VIA PHOTOISOMERIZATION
OF HETEROAROMATIC N-OXIDES:
3.1-BENZOXAZEPINE**



Submitted by ANGELO ALBINI, GIAN FRANCO BETTINETTI, and GIOVANNA MINOLI¹
Checked by PATRICK MACMANUS and ROBERT M. COATES

1. Procedure

Caution! 3,1-Benzoxazepine is a strong lacrimator and a moderate skin irritant. The preparation should be carried out in a well-ventilated hood. See benzene warning, *Org. Synth.* **1978**, 58, 168. The apparatus should be shielded to avoid exposure to ultraviolet light.

Irradiation is carried out in a round-bottomed, cylindrical, Pyrex vessel (Note 1) equipped with a Pyrex immersion well (Note 2), nitrogen inlet, distillation sidearm, a small sidearm fitted with a rubber septum for removing aliquots, and a magnetic stirring bar. The flask is charged with 12 g (0.066 mol) (Note 3) of quinoline *N*-oxide dihydrate (Note 4) and 1.3 L of dry benzene (Note 5). The mixture is stirred and heated to boiling with a heating mantle as a slow stream of nitrogen (Note 6) is bubbled into the vessel. Benzene is distilled through the sidearm until the distillate is perfectly clear (Note 7). The lamp (Note 8) is placed in the immersion well, water is circulated through the cooling jacket, and the nitrogen flow is adjusted as necessary to maintain an outward flow of gas while the light yellow solution cools to room temperature (Note 9). The solution is stirred vigorously (Note 10) and irradiated for 2.5–3 hr at which time the *N*-oxide is largely consumed (Note 11). The orange solution is transferred to a 1-L, round-bottomed flask, and the benzene is removed by rotary evaporation at room temperature. The red-orange oily residue which contains some solid is extracted with three 40-mL portions of dry cy-

clohexane, the combined cyclohexane extracts are evaporated under reduced pressure at room temperature, and the extraction operation is repeated on the oil thus obtained (Note 12). Evaporation of the combined cyclohexane extracts affords 6.1–6.3 g (63–65%) of crude 3,1-benzoxazepine (Note 13). Bulb-to-bulb distillation in a Kugelrohr apparatus at 0.2 mm with an oven temperature of 80°C affords 4.7–4.8 g (49–50%) of 3,1-benzoxazepine as a pale yellow oil, n_D^{24} 1.6074 (Notes 14 and 15).

2. Notes

1. The apparatus used by the checkers for irradiations at a 9-g scale was 33 cm high and 9 cm in diameter and had a 60/50 T joint at the top for the immersion well. The joints for the distillation and sampling sidearms were 24/40 and 14/20, respectively. The gas inlet was located about 6 cm from the bottom of the vessel to accommodate the use of a heating mantle. A disk of coarse, sintered glass was sealed into the gas inlet near its point of attachment. The capacity of the vessel with the immersion well in place was ca. 900 mL. The submitters used a similar but flat-bottomed apparatus of 1.2-L capacity. The flat-bottomed vessel facilitates vigorous stirring, but it does not fit as well into the heating mantle and may therefore be somewhat hazardous to use.

2. The checkers used a Vycor immersion well and a Pyrex filter sleeve. The immersion well, 450-W mercury lamp, and the requisite transformer are available from Hanovia Lamp Division, Canrad-Hanovia Inc, 100 Chestnut Street, Newark, NJ 07105.

3. The checkers carried out the irradiation on a 9-g scale in 750 mL of benzene after azeotropic distillation.

4. Quinoline *N*-oxide dihydrate is supplied by Aldrich Chemical Company, Inc. and EGA Chemie KG, Steinheim/Albuch, Germany. The submitters prepared the compound by the procedure of Hayashi² with minor modifications. The water of hydration may be removed under reduced pressure in a drying pistol. However, since the anhydrous *N*-oxide is very hygroscopic, the submitters have found that it is more expedient to use the dihydrate and remove the water by azeotropic distillation in the irradiation vessel.

5. The checkers dried the benzene by distillation from calcium hydride immediately before use. The submitters report that toluene may be

used instead of benzene; however, since the product is not very thermally stable, they advise that the toluene should be evaporated without heating during the isolation.

6. Other dry gases may be used. The submitters report that the reaction is not quenched by oxygen.

7. A total of ca. 150–300 mL was collected. The distillation time may be reduced by insulating the vessel and sidearm with glass wool.

8. The submitters used a Helios Italquartz 500-W lamp which has emission characteristics similar to those of the Hanovia 450-W medium pressure mercury lamp used by the checkers.

9. The checkers noticed that a thin film of oil which was evidently quinoline *N*-oxide deposited on the surface of the immersion well and irradiation vessel during cooling.

10. Vigorous stirring is essential for optimum yields. The checkers obtained lower isolated yields (ca. 32–33%) in two runs in which a relatively slow stirring rate was employed. The low yields were probably caused in part by deposition of oil on the surface of the immersion well and the resulting interference with the transmission of ultraviolet light into the solution.

11. The submitters emphasize the importance of terminating the irradiation before all of the *N*-oxide is consumed. Overirradiation gives rise to a more complicated mixture of products from which the product can no longer be isolated by the simple extraction procedure described.

The progress of the irradiation was determined by the checkers by proton NMR analysis. At appropriate intervals 5-mL aliquots were removed, the solvent was evaporated, and hexamethylbenzene was added as an internal standard. The ratio of *N*-oxide, benzoxazepine, and hexamethylbenzene was determined from integration of the resonances at δ 8.46 (d, 1 H, $J = 6$), 5.55 (d, 1 H, $J = 6$), and 2.26 (s, 18 H), respectively, in chloroform-*d*. After 2.5–3 hr of irradiation the amount of benzoxazepine present was ca. 60–68% of theoretical and ca. 10% of starting *N*-oxide remained.

The submitters followed the course of the irradiation by TLC analysis on silica gel with 5% (v/v) methanol in chloroform as developing solvent. Since some by-products have R_f values coincident with the *N*-oxide, this spot will not completely disappear and caution must be exercised to avoid overirradiation.

12. This extraction procedure separates most of the carbostyryl, that is, 2(1*H*)-quinolinone, which is formed to the extent of ca. 20% in the irradiation. The submitters have isolated the carbostyryl by-product by crystallization of the extraction residue from 95% ethanol in runs carried out to high conversion. Alternatively, the carbostyryl may be isolated by chromatography of the crude product on silica gel with 5% methanol-chloroform as eluant. However, the benzoxazepine cannot be obtained by this method since it undergoes hydrolysis during the chromatography.

13. The purity of the crude product is about 90% according to NMR analysis, the remaining material being mostly unchanged *N*-oxide.

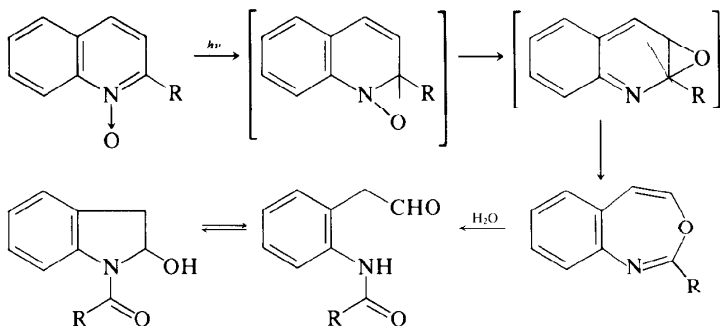
14. The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 1665 (C=N), 1630 (C=C), 1480 (sharp), 1440 (sharp), 1035 (strong), 765 (strong); ^1H NMR (CDCl_3) δ : 5.55 (d, 1 H, $J = 6$, CH=CH O), 5.84 (d, 1 H, $J = 6$, CH-CH-O), 6.44 (s, 1 H, O-CH=N), 6.96 (m, 4 H, aromatic protons).

15. Samples of the product stored in tightly stoppered flasks in a freezer at -20°C for several weeks showed no sign of decomposition.

3. Discussion

The preparation of 3,1-benzoxazepines by photochemical isomerization of quinoline *N*-oxides constitutes a rather general entry into this class of seven-membered heterocycles. Since the structure of the photoisomer of 2-phenylquinoline *N*-oxide was first recognized as 2-phenyl-3,1-benzoxazepine by Buchardt et al.,³ the scope of this method for oxidative ring expansion of six-membered heterocyclic *N*-oxides to 1,3-oxazepines has been extensively explored.⁴ For example, irradiation of 2-cyano-, 2-phenyl-, and 2-methoxyquinoline *N*-oxides affords the corresponding 2-substituted 3,1-benzoxazepines in 70–90% yield.⁵ However, isolation of the moisture-sensitive parent compound was only recently accomplished in the submitters' laboratories.⁶

Related 1,3-oxazepines have been obtained from irradiation of many other heterocyclic *N*-oxides including pyridine *N*-oxides, isoquinoline *N*-oxides, quinoxaline *N*-oxides, quinoxaline *N*-oxides, phenanthridine *N*-oxides, benzophenazine *N*-oxides, and acridine *N*-oxides.⁴ However, the reported yields are variable and have generally been higher for phenyl and other aryl-substituted derivatives.



A mechanism involving initial cyclization to an oxaziridine, [1,5] sigmatropic rearrangement to an imino epoxide, and electrocyclic ring opening was originally proposed for the photochemical isomerization.⁴ However, since later attempts to detect intermediates by flash photolysis were unsuccessful,⁷ ground-state oxaziridines, if formed at all, must have exceedingly short lifetimes. The benzoxazepines undergo facile hydrolysis to *o*-(*N*-acylamino)phenylacetaldehydes which frequently exist as the cyclic carbinol amide tautomers. If water is present during the irradiation from use of the *N*-oxide hydrate or moist solvent, the hydrolysis products may be isolated instead of the benzoxazepine. Dehydration of the carbinol amide to *N*-acyl indoles may also occur during irradiation and/or purification of the products. The formation of carbostyrils is sometimes an important competing reaction in the irradiation of quinoline *N*-oxides and this by-product is in fact formed to the extent of ca. 20% in the present procedure. The use of polar protic solvents such as water or alcohols favors carbostyryl formation in contrast to aprotic solvents such as benzene or acetone in which the pathway leading to benzoxazepines usually predominates.

1. Istituto di Chimica Organica dell'Università, v. le Taramelli 10, 27100 Pavia, Italy.
2. Hayashi, E., private communication to Ochiai, E., in "Aromatic Amine *N*-Oxides," Elsevier Publishing Co.: Amsterdam, 1967, p 24.
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4. (a) Spence, G. G.; Taylor, E. C.; Buchardt, O. *Chem. Rev.* **1970**, *70*, 231-265; (b) Bellamy, F.; Streith, J. *Heterocycles* **1976**, *4*, 1391-1447.
5. (a) Kaneko, C.; Yamada, S. *Chem. Pharm. Bull.* **1966**, *14*, 555-557; (b) Kaneko, C.; Yamada, S.; Ishikawa, M. *Tetrahedron Lett.* **1966**, 2145-2150; (c) Buchardt, O.; Kumler, P. L.; Lohse,

C. Acta Chem. Scand. **1969**, 23, 1155–1167; (d) Albini, A.; Fasani, E.; Dacrema, L. M. *J. Chem. Soc., Perkin Trans. I* **1980**, 2738–2742.

6. Albini, A.; Bettinetti, G. F.; Minoli, G. *Tetrahedron Lett.* **1979**, 3761–3764.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,1-Benzoxazepinc (8, 9); (15123-59-8)

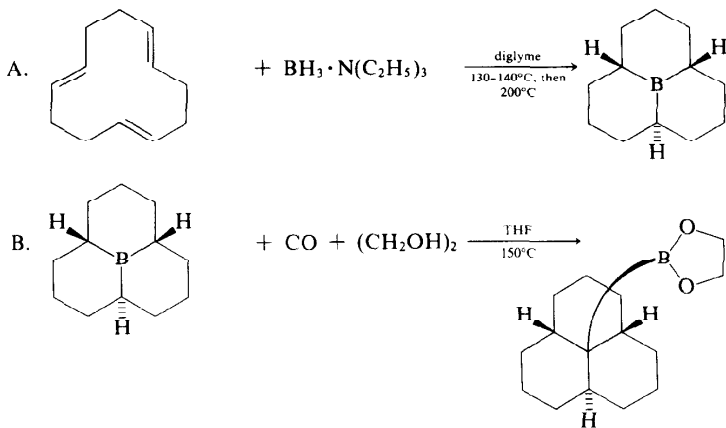
Quinoline *N*-oxide: Quinoline 1-oxide (8, 9); (1613-37-2)

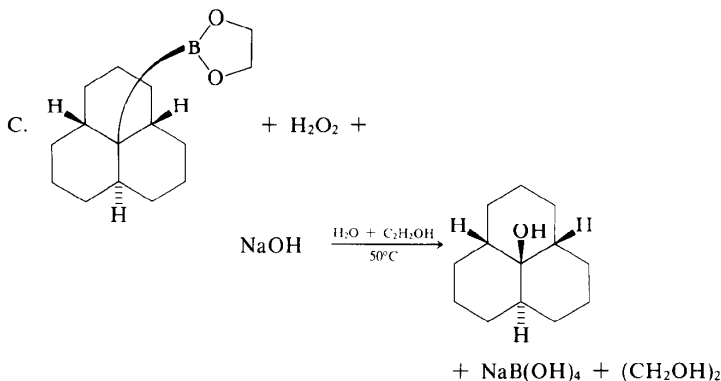
Hexamethylbenzenc: Benzenc, hexamethyl- (8, 9); (87-85-4)

Carbostyryl (8) (493-62-9); 2(1*H*)-Quinolinone (9) (59-31-4)

PERHYDRO-9b-BORAPHENALENE AND PERHYDRO-9b-PHENALENOL

(9b-Boraphenalene, dodecahydro-) and [Phenalen-9b α (2*H*)-ol,
3,3 α ,4,5,6,6 α ,7,8,9,9 β -decahydro-]





Submitted by EIICHI NEGISHI^{1,3} and HERBERT C. BROWN^{2,3}

Checked by A. J. COCUZZA and R. E. BENSON

1. Procedure

Caution! The products used and formed in Step A are extremely pyrophoric. Great care should be taken in conducting this step.

A. *cis,trans-Perhydro-9b-boraphenalene*. A 1-L, three-necked, round-bottomed flask is fitted with a septum, thermometer, magnetic stirring bar, and a 12-cm Vigreux column. A 2-L, two-necked receiving flask is attached to the Vigreux column and fitted with a nitrogen inlet tube that is attached to a mercury bubbler device to permit a positive pressure on the system (Note 1). The entire system is flushed with nitrogen and, while the system is maintained under a static pressure of nitrogen, 500 mL (0.050 mol) of a 1.0 *M* solution of borane in tetrahydrofuran (THF, Note 2) is added to the reaction flask by means of a syringe. The flask is immersed in an ice-water bath, stirring is begun, and 50.6 g (0.50 mol) of triethylamine (Note 3) is added slowly over 15 min. After the addition is completed, the THF is removed by distillation at atmospheric pressure and 300 mL of dry diglyme (Note 4) is added. The resulting solution is heated to 130–140°C and a solution of 81 g (0.50 mol) of *trans,trans,trans*-1,5,9-cyclododecatriene (Note 5) in 100 mL of dry diglyme (Note 6) is added over 2 hr. At the end of this time, the diglyme is removed by distillation at atmospheric pressure and the residual oil is

heated at 200°C for 6 hr (Note 7). After the reaction is cooled, the thermally treated product is used directly in Step B (Note 8). Product free of polymeric impurity can be obtained by distillation (Notes 9, 10).

B. cis,cis,trans-2-(Perhydro-9'b-phenalyl)-1,3,2-dioxaborole. The 250-mL pressure vessel (Note 11) is fitted with a cap bearing a rubber septum. Two hypodermic needles are inserted into the vessel through the septum, one with the end close to the bottom of the vessel and the other with the end close to the top. The vessel is flushed with nitrogen, with the exit gas passing through a mercury bubbler device. One-fifth of the thermally treated, undistilled product obtained from Step A is dissolved in 50 mL of dry THF (Note 12) and added to the vessel by means of a syringe while a static pressure of nitrogen is maintained on the vessel. Ethylene glycol (18.6 g, 16.8 mL, 0.30 mol) (Note 13) is then added. The rubber septum is removed and the vessel is quickly connected to a cylinder of carbon monoxide (Note 14) and placed in a heating device capable of agitation. The vessel is agitated and the pressure increased with carbon monoxide to ca. 70 atm (ca. 1000 psi); the temperature is raised to 150°C. The vessel is maintained at this temperature for 2 hr and then cooled to room temperature and opened to the air. The contents of the vessel are transferred to a flask; the vessel is rinsed with two 50-mL portions of pentane, and the pentane is added to the product. The resulting solution is washed with 50 mL of water and dried over magnesium sulfate. The drying agent is removed by filtration, and the pentane removed by distillation to give 19.4 g of *cis,cis,trans-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole*, a solid that can be further purified by recrystallization from pentane, mp 101–102°C (Note 15).

C. cis,cis,trans-Perhydro-9b-phenalenol. A 500-mL, three-necked, round-bottomed flask is fitted with a septum, thermometer, magnetic stirring bar, and a reflux condenser, which is connected to a nitrogen inlet and a mercury bubbler device. The system is flushed with nitrogen, and 50 mL of THF, 100 mL of 95% ethanol, and 19.4 g (0.0782 mol) of *cis,cis,trans-2-(perhydro-9'b-phenalyl)-1,3,2-dioxaborole* from step B are added to the flask together with 37 mL (0.220 mol, 120% excess) of 6 *N* sodium hydroxide. The solution is stirred and, by means of a dropping funnel, 37 mL (~0.326 mol) of 30% hydrogen peroxide (Note 16) is added at such a rate that the temperature of the reaction mixture does not exceed 40°C. After the initial reaction has subsided, the reaction mixture is heated for 2 hr at 50°C to assure complete oxidation (Note

17). At the end of this time, 300 mL of pentane is added. The mixture is transferred to a separatory funnel, and the organic layer is separated and washed three times with 50-mL portions of water and then dried over magnesium sulfate. The mixture is filtered, and the solvent is removed by distillation to yield a solid (Note 18) which is recrystallized from cold pentane to give 10.9 g (71.7%) of *cis,cis,trans*-perhydro-9b-phenalenol, mp 75–76°C (Note 19).

2. Notes

1. All joints must be well greased and securely clamped. Even a minor leak is a fire hazard.

2. The checkers used a reagent available from Aldrich Chemical Company, Inc. Borane–THF was prepared by the submitters.² The direct use of borane–THF for hydroboration results in the formation of a polymeric, insoluble intermediate, which can be depolymerized by heating.

3. The checkers refluxed triethylamine, available from Eastman Organic Chemicals, with phenyl isocyanate and then isolated the amine by distillation. The submitters used a reagent available from Aldrich Chemical Company, Inc.

4. The checkers used a reagent available from Aldrich Chemical Company, Inc. The diglyme was distilled from sodium benzophenone ketyl prior to use. The submitters used a reagent available from the same source and distilled it from lithium aluminum hydride prior to use.

5. The checkers and the submitters used reagent available from Chemical Samples Co. The submitters state that other isomers such as *trans,trans,cis*-1,5,9-cyclododecatriene or a mixture of isomers can be used.³ In this case a slightly different isomer distribution is observed, and the yields of isolated product are somewhat lower. The checkers confirmed this observation, using *trans,trans,cis* reagent available from Aldrich Chemical Company, Inc.

6. A syringe pump was used with the syringe well greased with a polyhalo hydrocarbon lubricant. Alternatively, a pressure-equalizing dropping funnel can be used.

7. It is essential to heat the initially formed product to 200°C to achieve isomerization of the other isomers present to *cis,trans*-perhydro-9b-boraphenalene. When this thermal treatment is omitted, the desired product is contaminated with one major (30–40%) and several minor, unidentified, isomeric substances.

8. Perhydro-9b-boraphenalene is highly flammable. The transfer must be carried out with caution. The use of gloves is recommended to avoid direct contact with the organoborane. The transfer is most conveniently done under a slightly positive pressure of nitrogen using a broad gauge (18G), double-tipped needle.

9. The crude product is diluted with a small amount of dry THF and the solution transferred to a 100-mL distillation flask. Distillation through a 12-cm Vigreux column gives 58.0–60.1 g (66–68% yield) of a mixture of *cis,trans*- and *cis,cis*-perhydro-9b-boraphenalene, bp 113–114°C (9.5 mm), ^1H NMR (CDCl_3) δ : 0.7–2.2.

10. The submitters state that the composition of the distillate is 92 : 8 *cis,trans* : *cis,cis* isomer, based on GC analyses using an SE-30 column. The assigned stereochemistry is supported by the ^1H NMR spectrum of the pyridine complex.³

11. The checkers used a 250-mL Hastelloy pressure vessel. The submitters used a 250-mL autoclave available from American Instrument Co.

12. The checkers used a reagent available from Fisher Scientific Company. The submitters used a reagent available from Aldrich Chemical Company, Inc.

13. The checkers distilled the reagent available from E.I. du Pont de Nemours & Co. The submitters used a reagent available from Aldrich Chemical Company, Inc.

14. The checkers and submitters used a reagent available from Matheson Gas Products.

15. The checkers obtained the product in 87% crude yield using distilled boraphenalene. Recrystallization from pentane gave product in 66% yield, mp 101–102°C, with the following spectral characteristics: IR (KBr) cm^{-1} : 1185, 1200, 1250, 1310, 1385, 2860, and 2900–2950; ^1H NMR (CDCl_3) δ : 1.0–1.9 (m, 21 H), 4.11 (s, 4 H). The structure of the product has been confirmed by X-ray crystallography.³

16. The checkers and the submitters used reagent available from Fisher Scientific Company.

17. The submitters state that oxidation of the dioxaborole is unusually sluggish and urge the use of ethanol as a cosolvent and an excess of 6 *N* sodium hydroxide. They also urge monitoring of the reaction by GC. The checkers monitored the reaction by both GC and TLC analyses. GC analysis by the checkers was conducted using the following column and conditions: 3.2-mm by 2-m column, 7% SE 30/3% Silar on Gas

Chrom Q (60–80 mesh), 170°C, 50 mL of nitrogen per min. The retention times for the perhydrophenalenol and dioxaborole are 6.4 and 15.2 min, respectively. For TLC analyses, Analtech silica gel plates bearing the material were eluted by 1 : 2 methylene chloride–petroleum ether, and visualized with phosphomolybdic acid: perhydrophenalenol, R_f 0.4; dioxaborole, R_f 0.9. The checkers found that the reaction was essentially complete after addition of the hydrogen peroxide. Additional heating did not lower the yield of product.

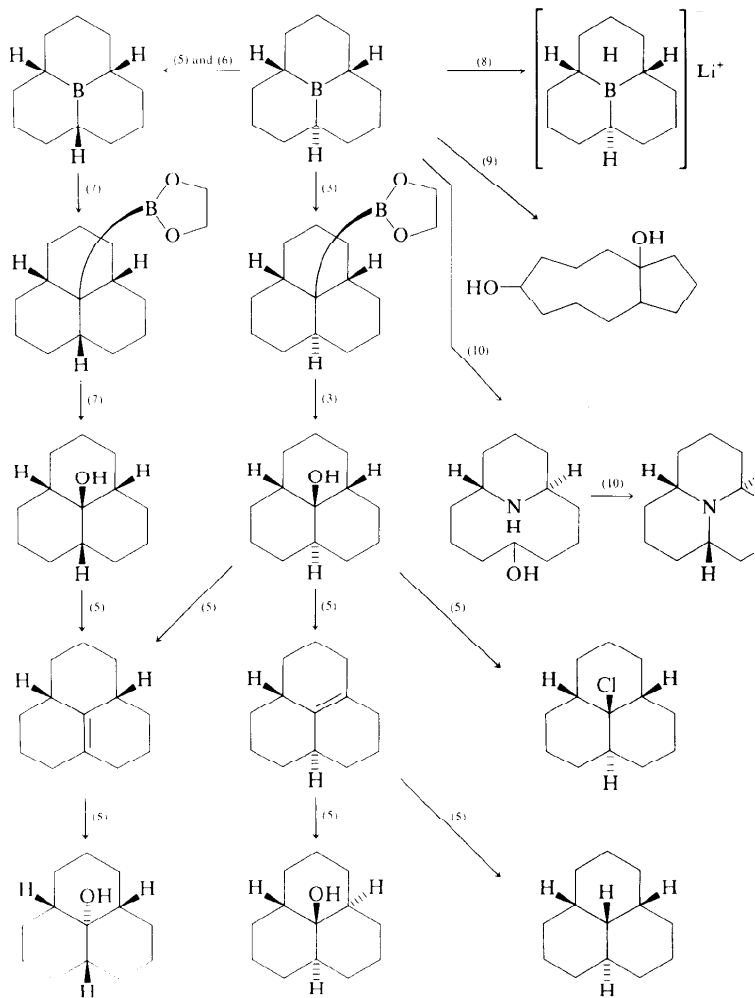
18. The submitters state that GC analysis of the solid indicates a 92 : 8 mixture of the *cis,cis,trans* and *cis,cis,cis* isomers.

19. Using recrystallized borazole from Step B, the checkers obtained product, recrystallized from pentane, mp 75–76°C, in 85% yield, having the following spectral characteristics: IR (KBr) cm^{-1} : 1450 (s), 2860 (m), 2930 (s), and 3460 (m); ^1H NMR (CDCl_3) δ : 1.0–2.3; ^{13}C NMR (CDCl_3) δ : 73.24 (s), 44.32 (d), 33.86 (d), 29.12 (t), 29.79 (t), 27.42 (t), 26.52 (t), 21.25 (t) (uncoupled spectrum).

3. Discussion

Preparation of the two stereoisomers of perhydro-9b boraphenalene was originally reported by Köster and Rotermund,⁶ and the present procedure (part A) is largely based on the procedure described by these authors. However, the original stereochemical assignment was incorrect and has been reversed.^{3,7} Furthermore, these authors did not use the thermal treatment described above, which appears essential to achieve isomerization of other constitutional isomers into perhydro-9b-boraphenalene.³ The original procedure for isomerization of the *cis,trans* isomer to the all *cis* isomer has been satisfactory. Contrary to the claim made by these authors,⁶ however, this isomerization does not lead quantitatively to the all *cis* isomer, but reaches an equilibrium, which consists of the all *cis* and *cis,trans* isomers in the ratio of 88 : 12; this ratio was also confirmed by reverse isomerization of the pure all *cis* isomer.⁵

cis,trans-Perhydro-9b-boraphenalene has been converted to lithium *cis,cis,trans*-perhydro-9b-boraphenyl hydride by reaction with lithium hydride.⁸ The tricyclic organoborane reported here has been converted to bicyclo[7.3.1]dodecane-1,5-diol⁹ and *trans*-13-azabicyclo[7.3.1]tridecan-5-ol.¹⁰ The latter has been converted to *cis,trans*-perhydro-9b-azaphenalene.¹⁰



Scheme 1

The procedure reported here (parts B and C) has been applied with minor modifications to the syntheses of the *cis,cis,cis* isomers of the 1,3,2-dioxaborole and perhydro-9b-phenalenol.⁷ The two other stereoisomers, *cis,trans,trans* and *trans,trans,trans*, have been prepared from *cis,cis,trans*-perhydro-9b-phenalenol via the *cis* and *trans* isomers of $\Delta^{3a,9b}$ -perhydrophenalene.⁵ In addition, a few isomers of perhydrophenalenol and of perhydrophenalene and *cis,cis,trans*-9b-chloroperhydrophenalene have also been prepared from *cis,cis,trans*-perhydro-9b-phenalenol.⁵ Some of the representative transformations are summarized in Scheme 1. (The numbers in parentheses refer to references.)

1. Department of Chemistry, Syracuse University, Syracuse, NY 13210. The current address is the same as Ref. 2.
2. Richard B. Wetherill Laboratory, Purdue University, West Lafayette, IN 47907.
3. The results described here were previously reported as a Communication: Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5478-5480. A similar procedure has also been described elsewhere.⁴
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Perhydro-9b-boraphenalene: 9b-Boraphenalene, dodecahydro- (8, 9); (16664-33-8); *cis,cis*-; (3 α , 6 α , 9 α), (1130-59-2); *cis,trans*-; (3 α , 6 α , 9 β), (2938-53-6)

Perhydro-9b-phenalenol: Phenalen 9b(2H) ol, decahydro-*cis,cis,trans*- (8); Phenalen-9b α (2H)-ol, 3,3 α ,4,5,6,6 α ,7,8,9,9 β -decahydro- (9); (16664-34-9)

Borane-tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1 : 1) (8, 9); (14044-65-6)

Triethylamine (8); Ethanamine, *N,N*-diethyl- (9); (121-44-8)

Diglyme: Ether, bis(2-methoxyethyl) (8); Ethane 1,1'-oxybis(2 methoxy)- (9); (111-96-6)

1,5,9-Cyclododecatriene (8, 9); (4904-61-4); *trans,trans,trans*:- (*E,E,E*)-; (676-22-2); *trans,trans,cis*:- (*E,E,Z*)-; (706-31-0); *trans,cis,cis*:- (*E,Z,Z*)-; (2765-29-9); *cis,cis,cis*:- (*Z,Z,Z*)-; (4736-48-5)

2-(Perhydro-9'b-phenalyl)-1,3,2-dioxaborole: Phenalene-9b(2*H*)-boronic acid, decahydro-, cyclic ethylene ester (8); (18604-57-4)

Ethylene glycol (8); 1,2-Ethanediol (9); (107-21-1)

Lithium perhydro-9b-boraphenyl hydride: Borate (1-), cyclododecane-1,5,9-triylhydro-, lithium (8); Borate (1-), 1,5,9-cyclododecane triylhydro-, lithium (T-4)- (9); (36005-35-3)

Bicyclo[7.3.0]dodecane-1,5-diol: 3a,7(1*H*)-Cyclopentacyclononenediol, decahydro- (9); (52318-91-9)

13 Azabicyclo[7.3.1]tridecan 5 ol, stereoisomer (9); (61714-12-3)

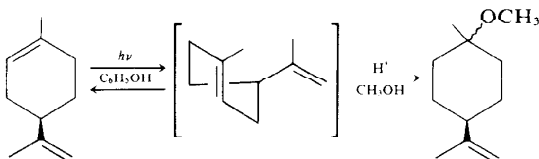
Perhydro-9b-azaphenalene: Pyrido(2,1,6-*de*)quinolizine, dodecahydro- (9); *cis,cis*:- (3a α ,6a α ,9a α)-; (57147-57-6); *cis,trans*:- (3a α ,6a α ,9a β)-; (57194-67-9)

Perhydrophenalene: 1*H*-Phenalene, dodecahydro- (8); (2935-07-1); 1*H*-Phenalene, dodecahydro-, (3a α ,6a α ,9a α ,9b β)- (9); (40250-64-4)

9b-Chloroperhydrophenalene: Phenalene, 9b α -chloro-2,3,3a α ,4,5,6,6a α ,7,8,9,9a β ,9b-dodecahydro- (8); (33343-40-7); 1*H*-Phenalene, 9b-chlorododecahydro-, *cis,cis,trans*:- (3a α ,6a α ,9a α ,9b β)- (9); (52079-56-8)

**PHOTOPROTONATION OF CYCLOALKENES:
LIMONENE TO *p*-MENTH-8-EN-1-YL
METHYL ETHER**

(Cyclohexene, 1-methyl-4-(1-methylethenyl)-) to (Cyclohexane, 1-methoxy-
1-methyl-4-(1-ethenyl-1-methyl-))



Submitted by F. P. TISE and P. J. KROPP¹
Checked by R. L. AMEY and R. E. BENSON

1. Procedure

A 250-mL photochemical reactor (see Figure 1) is fitted with a cylindrical Vycor filter sleeve, a 450-W Hanovia mercury lamp, and a water-cooled condenser which is connected to a mineral oil bubbler. Tubing attachments are made so that water is circulated through the condenser and then through the Vycor filter sleeve. The tube leading from the bottom of the reaction vessel and containing the glass frit is connected in series to a trap fitted with a fritted filter stick and then to a trap that is connected to a nitrogen source. The system is flushed with nitrogen, and sufficient anhydrous methanol is placed in the trap containing the fritted stick to provide for a methanol-saturated gas stream during the course of the reaction (Note 1).

The nitrogen-flushed reactor is charged with a solution of 20.0 g (147 mmol) of (+)-limonene (Note 2), 5.0 g (53 mmol) (Note 3) of phenol, and 5 drops of concentrated sulfuric acid in 210 mL (167 g, 5.2 mol) of anhydrous methanol (Note 4). Water flow through the condenser is started (Note 5), and the nitrogen flow is adjusted to provide good agitation of the contents of the vessel. After 15 min, irradiation is started and the reaction followed by GLC (Note 6), with 48 hr being the approximate time needed for essentially complete conversion (Note 7).

The solution is poured into 900 mL of 5% aqueous sodium hydroxide solution containing 125 g of sodium chloride, and the mixture is extracted with two 100-mL portions of ether. The ether layers are combined, washed with 50 mL of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated with a Buchi rotary evaporator. After a preliminary distillation to separate the product from a small amount of non-volatile material, the liquid is distilled at reduced pressure through a Teflon spinning band column (47 cm \times 7 mm). The material that distills at 90–95°C (10 mm) is collected to give 12.8–13.2 g (52–53%) of a mixture of *cis*- and *trans*-*p*-menth-8-en-1-yl methyl ether (Notes 8–10).

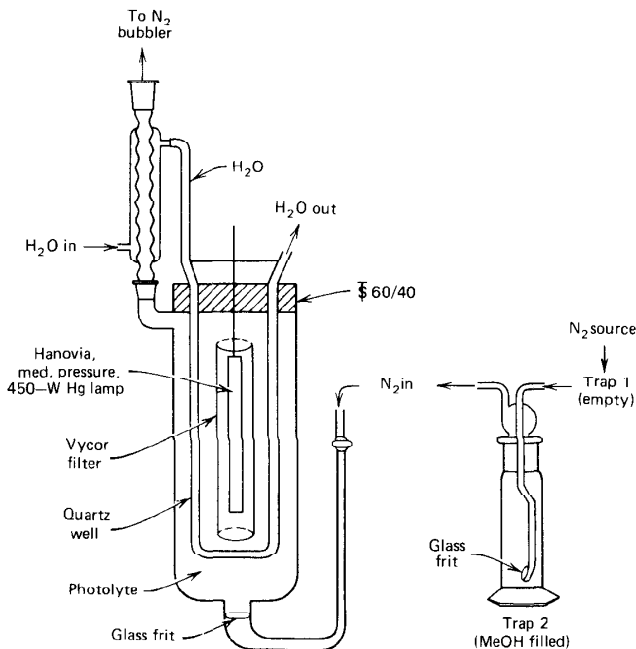


Figure 1

2. Notes

1. The submitters used a reactor with a joint which was capped with a rubber septum fitted with two syringe needles, which were attached by means of a Y-tube to a single nitrogen line. To one of these needles is attached a piece of 1.70-mm O.D. polyethylene tubing of sufficient length to reach to the bottom of the reaction vessel. By use of pinchcocks, nitrogen can be passed through either of the two needles. The solution was stirred with a magnetic stirring bar.

2. (+)-Limonene was obtained from Aldrich Chemical Company, Inc. and distilled before use.

3. The checkers used reagent available from Fisher Scientific Company.

4. The checkers used fresh, acetone-free, absolute methanol available from Fisher Scientific Company.

5. For best results the cooling water should pass through the condenser first and then through the immersion well. This arrangement lessens evaporation of methanol.

6. The submitters used a 3-m \times 3.2-mm stainless steel column packed with 20% SF-96 on Chromasorb W (60–80 mesh) and a He flow rate of 60 mL/min. With a temperature program of 4 min at 50°C followed by an increase of 10°C per min to a maximum of 200°C, the retention times were 17.9 and 18.7 min.

7. The checkers found that the reaction was impeded by the formation of a yellow film on the immersion well with very little further conversion occurring after 30 hr of irradiation.

8. The checkers used a 2.4-m \times 3.2-mm column packed with 7% SE-30 and 3% Silar on Chromasorb W (60–80 mesh) at 160°C. The retention time was 1.56 min for the trans isomer and 1.81 min for the cis isomer at a He flow rate of 55 mL/min.

9. The spectral properties of the product (approximately 60% cis : 40% trans isomers) are as follows: IR (neat) cm^{-1} : 3080 ($=\text{C}-\text{H}$); 2964, 2939, 2860, 2825, ($\text{C}-\text{H}$); 1645 ($\text{C}=\text{C}$); 1464, 1453, and 1442 (overlapping peaks); 1270, 1124, and 1082 ($\text{C}-\text{OC}$); 885 ($=\text{CH}$). ^1H NMR (CDCl_3) δ : 1.19 [s, 3 H, CH_3 (cis)], 1.30–2.00 (8 H, — (cis/trans)], 3.14 [s, 3 H, OCH_3 (trans)], 3.21 [s, 2 H, $=\text{CH}_2$ (cis/trans)].

10. The submitters state that similar irradiation of 20.0 g of cyclo-

hexene, 5.0 g of phenol, and 1.5 mL of concentrated sulfuric acid for 24 hr afforded cyclohexyl methyl ether in 70% yield.

3. Discussion

Acid-catalyzed, ground state additions to limonene generally afford a mixture of products resulting from competing protonation of both double bonds.² In one case in which selective reaction was observed, attack occurred at the acyclic C₈-C₉ double bond.³

The photoprotonation of cycloalkenes, described in this procedure, is believed to proceed via initial light-induced *cis* → *trans* isomerization of the alkene.⁴ The resulting highly strained *trans* isomer undergoes facile protonation. This procedure permits the protonation of cyclohexenes and cycloheptenes under neutral or mildly acidic conditions.⁵ Since the process is irreversible, high levels of conversion to addition products can be achieved.

Photoprotonation is generally specific for cyclohexenes and cycloheptenes. Smaller-ring cycloalkenes are incapable of undergoing *cis* → *trans* isomerization, and the *trans* isomers of larger-ring or acyclic analogues have insufficient strain to undergo ready protonation. Thus, in addition to facilitating protonation of cycloalkenes, the procedure affords a means of selectively protonating a double bond contained in a six- or seven-membered ring in the presence of another double bond contained in an acyclic, exocyclic, or larger-ring cyclic environment.⁶ When conducted in non-nucleophilic media, the photoprotonation procedure is also useful for effecting the isomerization of 1-alkylcyclohexenes and -heptenes to their exocyclic isomers.⁴

1. Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514.
2. For a review of the chemistry of limonene, see Verghese, J. *Perfum. Essent. Oil Rec.* **1968**, 59, 439-454.
3. Kuczynski, I.; Kuczynski, H. *Rocz. Chem.* **1951**, 25, 432-453.
4. For recent reviews of the photochemistry of alkenes see Kropp, P. J. *Mol. Photochem.* **1978**, 9, 39-65 and *Organic Photochemistry* **1979**, 4, 1-142.
5. There is a fine balance between the acidity of the alcohol and the basicity of the *trans*-olefin. For example, 1-methylcyclohexenes undergo photoprotonation in methanol whereas cyclohexenes require the addition of small amounts of acid. In the present example, the addition of a small quantity of acid reduces the competing formation of the exocyclic isomer, *p*-mentha-1(7),8-diene.
6. For an earlier report on the photoprotonation of (+)-limonene, see Kropp, P. J. *J. Org. Chem.* **1970**, 35, 2435-2436.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

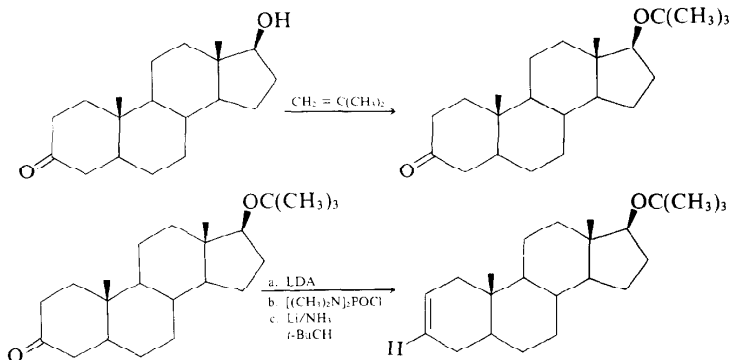
Limonene: (+)-*p*-Mentha-1,8-diene (8); Cyclohexene, 1-methyl-4-(1-methylethenyl)- (9); (5989-27-5)

Methanol (8, 9); (67-56-1)

cis-p-Menth-8-en-1-yl methyl ether: Ether, *p*-menth-8-en-1-yl methyl, *cis*- (8); Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl)- *cis*- (9); (24655-71-8)

trans-p-Menth-8-en-1-yl methyl ether: Ether, *p*-menth-8-en-1-yl methyl, *trans*- (8); Cyclohexane, 1-methoxy-1-methyl-4-(1-ethenyl-1-methyl)-, *trans*- (9); (24655-72-9)

REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES: PREPARATION OF 17 β -*tert*- BUTOXY-5 α -ANDROST-2-ENE



Submitted by ROBERT E. IRELAND, THOMAS H. O'NEIL, and GLEN L. TOLMAN¹
Checked by M. F. SEMMELHACK and JAMES W. HERNDON

1. Procedure

A. *Protection of the 17-hydroxyl group.* A solution of androst-4-en-17-ol-3-one (Note 1, 4.10 g, 14 mmol) in 30 mL of dichloromethane in a 250-

mL, one-necked round-bottomed flask equipped with a magnetic stirring bar and a rubber septum bearing two syringe needles (argon inlet and exit) is cooled to -20°C (refrigerated bath). Argon is allowed to pass over the surface of the mixture for 15 min and then boron trifluoride etherate (Note 2, 0.125 mL, 0.90 mmol) is added rapidly, via syringe, followed by anhydrous phosphoric acid (Note 3, 0.053 mL, 1.0 mmol). Isobutene (Note 4) is added as a gas through a large-bore syringe needle until approximately 100 mL has condensed. The steroid precipitates during addition of the isobutene and redissolves as the reaction proceeds. The drying tube is replaced with a stopper, the tightly sealed flask is allowed to warm to 25°C , and the mixture is stirred at this temperature for 4 hr (Note 5). The flask is cooled to 0°C , opened, and warmed to 25°C to allow excess isobutene to evaporate. The residue is poured into 2 *N* aqueous ammonium hydroxide (100 mL) and ethyl acetate (75 mL) is added. After the layers are vigorously shaken, the aqueous solution is washed with a second portion of ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue is recrystallized from hexane to give colorless crystals, mp $146\text{--}148^{\circ}\text{C}$, 4.10 g (86%, Note 6).

B. Preparation of N,N,N',N' -tetramethyldiamidophosphorochloridate. In a dry, 2-L, three-necked flask equipped with overhead stirrer, thermometer, argon outlet, and pressure-equalizing addition funnel is placed 400 mL of diethyl ether (Note 7). The flask is cooled in an isopropyl alcohol/dry ice bath while 100 g (2.2 mol) of anhydrous dimethylamine is added in one portion. A solution of 85 g (0.56 mol) of phosphoryl chloride in 200 mL of diethyl ether is added at a rate to maintain the temperature at $-35 \pm 5^{\circ}\text{C}$. The addition time is approximately 1.5 hr. After the addition is complete, the bath is removed, and stirring is continued for 4 hr. The thick white slurry is filtered through a coarse frit and the filter cake is washed with 4000 mL of diethyl ether. The combined filtrates are concentrated under aspirator pressure on a rotary evaporator. Fractional distillation of the concentrate through a 10-cm Vigreux column gives 71–80 g (74–84%) of the N,N,N',N' -tetramethyldiamidophosphorochloridate, bp $58.5\text{--}59^{\circ}\text{C}$ (0.6 mm) (Note 8).

C. Preparation and reductive cleavage of the vinyl phosphoroimide. A dry, 250 mL flask equipped with magnetic stirrer, syringe port (Note 9), and argon outlet is flushed three times with argon. To the flask

are added 40 mL of dry tetrahydrofuran (THF) and 1.17 mL (8.4 mmol) of dry diisopropylamine (Note 10). The flask is cooled in an acetone/dry ice bath while 7.4 mmol of butyllithium in hexane (Note 11) is added dropwise with stirring. After the addition is complete, the solution is allowed to warm for 15 min. The flask is then cooled in an ice/water bath. To this solution is added 1.61 g (4.6 mmol) of 17 β -*tert*-butoxy-5 α -androstan-3-one in 30 mL of 2 : 1 THF/hexamethylphosphorotriamide solution. The reaction mixture is stirred with ice cooling for 15 min. *N,N,N',N'*-Tetramethyldiamidophosphorochloridate, 5.83 mL (0.038 mol), is added dropwise with stirring. After 15 min, the bath is removed; the flask is allowed to warm to 25°C and is stirred for an additional 2 hr. The excess reagent is hydrolyzed by slow addition of 30 mL of saturated aqueous sodium bicarbonate solution and stirring for 30 min. After three extractions with 100-mL portions of diethyl ether, the combined organic layers are washed twice with 100 mL water and 100 mL of saturated sodium chloride solution. The solution is dried over anhydrous magnesium sulfate and the ether is removed under reduced pressure on a rotary evaporator to afford 2.9–3.0 g of a crude yellow solid (Note 12). The crude phosphoroamidate is dissolved in 40 mL of dry THF and added to a dry, three-necked, 250-mL flask equipped with overhead stirrer, cold finger condenser (acetone/dry ice), argon bubbler, and acetone/dry ice bath. Dry ammonia is distilled into the flask until the phosphorodiamidate begins to precipitate. The bath is removed and the solution is allowed to warm to reflux. Dry *tert*-butyl alcohol (1.75 mL, Note 13) is added in one portion. To the clear solution is added 1.5 cm of $\frac{1}{8}$ -in., cleaned lithium wire in 0.3-cm portions. The blue color is maintained (by the addition of lithium wire if necessary) with stirring for 2 hr. Sodium benzoate is added in 25-mg portions until the blue color is discharged. Ammonium chloride (0.50 g) is added in one portion, the condenser removed, and the ammonia allowed to evaporate. The residue is taken up in 100 mL of diethyl ether and 100 mL of water. The layers are separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are washed with 100 mL of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. The ether is removed under reduced pressure on a rotary evaporator. The crude olefin is filtered through 15 g of silica gel (Note 14) using benzene/ethyl acetate (2 : 1) as eluant, to give an off-white solid that is recrystallized from a minimum amount of absolute ethanol

to give, after drying, 1.1–1.2 g (71–78%) of 17 β -*tert*-butoxy-5 α -androst-2-ene, mp 115–117°C (Note 15).

2. Notes

1. Androstanolone was obtained from Aldrich Chemical Company, Inc., and used without purification.

2. Boron trifluoride etherate was distilled before use.

3. Anhydrous phosphoric acid was prepared by slow addition of 5 g of 15% phosphoric acid to 2 g of phosphorus pentoxide.²

4. Isobutene, reagent grade, was obtained from Phillips Company.

5. The flask was stoppered with a greased T 24/40 ground-glass stopper held in place by rubber bands stretched over appropriately placed wire hooks. The pressure at 25°C was slightly more than 1 atm.

6. The spectral properties are as follows: ¹H NMR (CDCl₃) δ : 0.74 (s, 3 H), 1.02 (s, 3 H), 1.13 (s, 9 H), 3.36 (m, 1 H); IR (CHCl₃) cm⁻¹: 1715 (C=O), 1255, 1205.

7. Diethyl ether (anhydrous) from Mallinckrodt Inc., dimethylamine (anhydrous from Eastman Chemical Co.) and phosphoryl chloride "Baker Analyzed Reagent" from J. T. Baker Chemical Co. were used without further purification.

8. Physical and spectral data are as follows: *d* 1.126; IR (neat) cm⁻¹: 1470, 1450, 1290, 1230, 980; ¹H NMR (neat) δ : 2.69 (d, *J*_{P-H} = 13).

9. All solutions were added via glass syringes under rigorously anhydrous conditions.

10. Diisopropylamine and hexamethylphosphorotriamide (Aldrich Chemical Company, Inc.) were distilled from calcium hydride.

11. Butyllithium in hexane was obtained from Alfa Products, Ventron Corporation or Foote Mineral Company. The checkers titrated the solution before³ use.

12. Spectral data are as follows: IR (CCl₄) cm⁻¹: 1660, 1350, 1215; ¹H NMR (CDCl₃) δ : 0.69 (s, 3 H, CH₃), 0.78 (s, 3 H, CH₃), 1.11 (s, 9 H, CH₃), 2.60 (d, 3 H, *J*_{P-H} = 10, N—CH₃), 3.28 (m, 3 H, CH₃O), 5.12 (m, 2 H, C=CH₂).

13. *tert*-Butyl alcohol was dried by distillation from calcium hydride.

14. Silica gel 60 (particle size 0.063–0.200 μ m) is available from E. Merck, A.G.

15. Spectral data are as follows: ¹H NMR (CDCl₃) δ : 0.63 (s, 3 H,

CH_3), 0.67 (s, 3 H, CH_3), 1.02 (s, 9 H, CH_3), 3.28 (s, 1 H, OCH), 5.43 (m, 2 H, vinyl H); IR (CHCl_3): The product was characterized by cleavage of the *tert*-butyl ether ($\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 , 0°C) to give 17β -hydroxy-5 α -androst-2-ene, mp 161 – 162°C , lit.⁴ mp 163 – 165°C .

3. Discussion

The reduction of a carbonyl group to an olefin has been accomplished by the Shapiro modification⁵ of the Bamford-Stevens reaction and by the hydride reduction of the corresponding enol ether,⁶ enol acetate,⁷ or enamine.⁸ The nickel reduction of the thioketal has also been used successfully.⁹

The lithium/amine reduction of N,N,N',N' -tetramethylphosphorodiamidates is a general method for the cleavage of the C–O bond.¹⁰ In addition to the reductive deoxygenation of carbonyl compounds to generate olefins, the phosphorodiamidates of alcohols are reduced in high yield to give alkanes. Alcohols in which the hydroxyl group is greatly hindered could be unreactive toward N,N,N',N' -tetramethyldiaminophosphorochloridate. In such cases, treatment of the alcohols with butyllithium and N,N -dimethylphosphoramidic dichloride in 1,2-dimethoxyethane and N,N,N',N' -tetramethylethylenediamine followed by addition of dimethylamine gave rise to N,N,N',N' -tetramethylphosphorodiamidates in good yields.¹¹ Combined in a two-step process (e.g., $\text{RCOR}' \rightarrow \text{RCHOHR}' \rightarrow \text{RCH}_2\text{R}'$), the method allows the reductive removal of a carbonyl functionality. This two-step process compares favorably with the analogous Wolff-Kishner reduction. Additionally, reduction of the enol phosphorodiamidate by dialkyl cuprate reagents generates a substituted olefin.¹²

The phosphorodiamidate group can also serve as a protecting group for the hydroxyl function, since it is stable to CH_3Li , LiAlH_4 , KOH , and $0.2\text{ }N$ aqueous HCl , but is quantitatively cleaved by butyllithium/TMEDA (tetramethylethylenediamine).¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Androstanolone: 5 α -Androstan-3-one, 17 β -hydroxy- (8); Androstan-3-one, 17-hydroxy-, (5 α ,17 β)- (9); (521-18-6)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃) (1 : 1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1 : 1) (9); (109-63-7)

Phosphorus pentoxide: Phosphorus oxide (8, 9); (1314-56-3)

Isobutene: Propene, 2-methyl- (8); 1-Propene, 2-methyl- (9); (115-11-7)

Phosphorus oxychloride [POCl₃]: Phosphoryl chloride (8, 9); (10025-87-3)

Dimethylamine (8); Methanamine, *N*-methyl- (9); (124-40-3)

N,N,N',N'-Tetramethyldiamidophosphorochloridate: Phosphorodiamidic chloride, tetramethyl- (8, 9); (1605-65-8)

Diisopropylamine (8); 2-Propanamine, *N*-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl (8, 9); (109-72-8)

Hexamethylphosphorictriamide: Phosphoric triamide, hexamethyl- (8, 9); (680-31-9)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

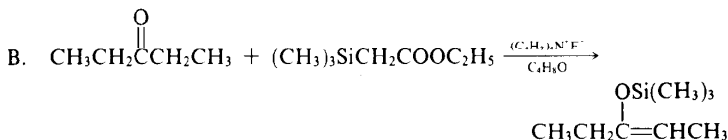
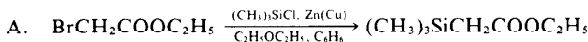
17 β -Hydroxy-5 α -androst-2-ene: 5 α -Androst-2-en-17 β -ol (8); Androst-2-en-17-ol, (5 α ,17 β)- (9); (2639-53-4)

N,N-Dimethylphosphoramidic dichloride: Phosphoramidic dichloride, dimethyl- (8, 9); (677-43-0)

N,N,N',N'-Tetramethylethylenediamine: Ethylenediamine, *N,N,N',N'*-tetramethyl- (8); 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl- (9); (110-18-9)

**SILYLATION OF KETONES WITH ETHYL
TRIMETHYLSILYLACETATE: (Z)-3-
TRIMETHYLSILOXY-2-PENTENE**

(Silane, [(1-ethyl-1-propenyl)oxy]trimethyl-, (Z)-)



Submitted by ISAO KUWAJIMA, EIICHI NAKAMURA, and KOICHI HASHIMOTO¹
Checked by PETER J. CARD and RICHARD E. BENSON

1. Procedure

Caution! Ethyl bromoacetate is intensely irritating to eyes and skin. The preparation of this ester should be carried out in an efficient hood.

A. *Ethyl trimethylsilylacetate* (Note 1). In a 3-L, three-necked flask fitted with a 1-L pressure-equalizing dropping funnel, mechanical stirrer, and efficient condenser which is connected to a nitrogen source are placed 97.5 g (1.5 mol) of zinc powder (Note 2) and 14.9 g (0.15 mol) of cuprous chloride (Note 3). After the reaction vessel is flushed with nitrogen, a static nitrogen atmosphere is maintained for the remainder of the reaction. A mixture of 150 mL of ether (Note 4) and 550 mL of benzene (Note 5) is added to the flask, and the resulting mixture is refluxed with stirring for 30 min with the aid of an electric heating mantle. Heating is discontinued and a solution of 109 g (128 mL, 1.0 mol) of chlorotrimethylsilane (Note 6) and 184 g (123 mL, 1.1 mol) of ethyl bromoacetate (Note 7) in a mixture of 90 mL of ether and 350 mL of benzene is promptly added through the dropping funnel at such a rate as to maintain the reaction at gentle reflux. The addition takes about 1 hr. After the addition is complete, the mixture is heated at reflux for 1 hr and then cooled in an ice bath. While the mixture is stirred, 300 mL of aqueous 5% hydrochloric acid is added through the dropping funnel over a 10-min period. The liquid layer is decanted into a 3-L separatory funnel and

the flask is washed with two 100-mL portions of ether. The ether solutions are added to the separatory funnel, the organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of ether. The organic phases are combined and washed twice with 200-mL portions of saturated aqueous sodium chloride, twice with 200-mL portions of saturated aqueous sodium bicarbonate, and finally with 200 mL of saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, the mixture is filtered, and the filtrate is concentrated on a rotary evaporator to a volume of about 400 mL. The residual yellow liquid is distilled in a 30-cm vacuum-jacketed Vigreux column at atmospheric pressure until the boiling point is 90°C. The remaining liquid is distilled at reduced pressure to give, after a small forerun, 101–118 g (63–74%, Note 8) of ethyl trimethylsilylacetate, bp 93–94°C (104 mm), n_D^{20} 1.4152–1.4154 (Note 9).

B. (Z)-3-Trimethylsiloxy-2-pentene. In a dry, 200-mL flask (Note 10) equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock, one exit of which is capped with a small rubber septum, is quickly placed 1.5 g (ca. 6 mmol) of dried tetrabutylammonium fluoride hydrate (Note 11). With the aid of a hypodermic syringe, 50 mL of dry tetrahydrofuran (THF, Note 12) is added through the septum, and the clear solution is stirred. After 5 min, the reaction vessel is immersed in a hexane/dry ice bath, and 38.4 g (0.240 mol) of ethyl trimethylsilylacetate is added during 10 min through a syringe which is rinsed with 15 mL of dry THF. After 10 min a solution of 17.2 g (0.200 mol) of 3-pentanone (Note 13) in 15 mL of dry THF is introduced during 10 min to the stirred solution with the aid of a syringe, which is then rinsed with 5 mL of dry THF. The clear solution is stirred for 3 hr, then warmed gradually to 0°C over about 1 hr and finally the temperature is held at 0°C for 2–4 hr (Note 14). Meanwhile, 400 mL of pentane (Note 15) in a dry, nitrogen-filled, 1-L flask equipped with a drying tube and a magnetic stirring bar is cooled with stirring in a hexane/dry ice bath, and the dark orange reaction mixture is poured into it. The reaction vessel is rinsed with three 50-mL portions of pentane. The pentane rinses are added to the reaction solution and the resulting mixture is filtered through a pad of Hyflo Super Cell on a sintered-glass filter, and the filtrate is washed with 100 mL of saturated aqueous sodium bicarbonate and 100 mL of saturated aqueous sodium chloride. The organic layer is dried over magnesium sulfate, the drying agent is removed by filtration, and the resulting solution is concentrated on a rotary evaporator at room temperature to a

volume of 150 mL. The remaining liquid is distilled through a 10-cm Vigreux column. After a very small amount of forerun (<1 g), 21.9–24.1 g (69–76%) of 3-trimethylsiloxy-2-pentene is obtained, bp 139–142°C; n_D^{20} 1.4133–1.4135 (Note 16).

2. Notes

1. This procedure is based on a report by Fessenden and Fessenden.^{2a} Cuprous chloride³ is a more efficient initiator than iodine as specified in the original procedure.

2. The submitters used zinc powder purchased from Koso Chemical (Japan) without any purification. The checkers used product available from Fisher Scientific Company. It is essential to use excess zinc to ensure complete consumption of ethyl bromoacetate which interrupts the catalytic cycle in step B of the present silylation reaction.

3. The submitters used cuprous chloride purchased from Koso Chemical Co. Ltd. without purification. The checkers used cuprous chloride available from Fisher Scientific Company.

4. The submitters used diethyl ether, obtained from Showa Ether, after distillation from sodium wire. The checkers distilled the product obtained from Fisher Scientific Company from lithium aluminum hydride.

5. Benzene was distilled over sodium wire before use.

6. The submitters used chlorotrimethylsilane obtained from Nakarai Chemical. The material was distilled from calcium hydride or sodium wire before use. The checkers used product available from Aldrich Chemical Company, Inc.

7. The submitters used ethyl bromoacetate (GR grade) obtained from Tokyo Kasei and distilled it before use in an efficient hood. The checkers used product available from Aldrich Chemical Company, Inc.

8. The submitters state that the yield ranged from 68 to 70% for runs made on a 1.5-mol scale.

9. Ethyl trimethylsilylacetate is stable to the usual manipulations, and can be stored in glass containers for years without change of physical and spectral properties. IR (liquid film) cm^{-1} : 1720, characteristic of α -silyl esters. The reported physical constants are bp 76–77°C (40 mm), n_D^{25} 1.4136,^{2a} n_D^{20} 1.4149.^{2b} ^1H NMR (CCl_4) δ : 0.17 (s, 9 H, CH_3Si), 1.31 (t, 3 H, $J = 7$, CH_3CH_2), 1.88 (s, 2 H, SiCH_2), and 4.14 (q, 2 H, $J = 7$, CH_2O).

10. Tetrabutylammonium fluoride is very hygroscopic. A drybox may be used to avoid rapid manipulation of the fluoride in the atmosphere and exposure of the reagent in the storage vessel to moisture. Alternatively, hydrated tetrabutylammonium fluoride (Note 11) can be dried in the reaction vessel and used directly.

11. Tetrabutylammonium fluoride trihydrate obtained from Fluka AG was dried over phosphorus pentoxide for 48 hr at a pressure of ~ 0.1 mm. The hygroscopic fluoride was pulverized with the aid of a spatula in a dry atmosphere. The checkers prepared the dry salt by this method using material obtained from Tridom Chemical, Inc.

Alternatively, the fluoride can be prepared as follows: A 10–40% aqueous or alcoholic solution of tetrabutylammonium hydroxide available from several sources is placed in a glass flask fitted with a Teflon-coated magnetic stirring bar and stirred gently. The pH of the solution is adjusted to about 8 by rapid addition of an almost theoretical amount of 48% aqueous hydrofluoric acid with the aid of a plastic pipet. *Caution: Hydrofluoric acid in contact with the skin produces extremely painful burns. Long, acid-resistant gloves should be worn.* Final adjustment of the pH to 7–8, measured with a pH meter, is achieved by addition of 5% aqueous acid. The bulk of the solvent is removed by distillation on a rotary evaporator at $\sim 30^\circ\text{C}$ (1 mm). The resulting white paste is further dried as described above to give the salt as a white mass.

The submitters state that in some cases, probably depending on the source of the hydroxide, the dried salt did not solidify. On such an occasion, the aqueous solution was diluted with deionized water to obtain a ~ 0.5 M aqueous solution. The resulting solution was cooled to $5\text{--}10^\circ\text{C}$ and allowed to stand to give a white clathrate. The supernatant liquid was removed by a pipet and the clathrate was washed once with cold water. When the clathrate was dried as described above the fluoride was obtained as a solid.⁴

12. Tetrahydrofuran was distilled successively from cuprous chloride and sodium wire,⁵ and further purified by distillation from sodium benzophenone ketyl in a recycling still. The checkers used product obtained from Fisher Chemical Company that was distilled from lithium aluminum hydride prior to use.

13. 3-Pentanone obtained from Tokyo Kasei (GR grade) was distilled before use. The checkers used product available from Aldrich Chemical Company, Inc.

14. The reaction is normally complete at -78°C , affording a product of 99.5% isomeric purity. It is advisable, however, to raise the reaction temperature finally to 0°C , since some unknown factors occasionally retard this catalyzed reaction. Development of an orange to red color of the mixture usually indicates the progress of the reaction.

15. Pentane was stored over sodium wire. The checkers used product available from Eastman Organic Chemicals.

16. The spectral properties of 3-trimethylsiloxy-2-pentene are as follows: ^1H NMR (CCl_4) δ : 0.18 (s, 9 H, SiCH_3), 1.03 (t, 3 H, $J = 7$, CH_3CH_2), 1.48 (d of t, 3 H, $\text{CH}_3\text{C}=\text{CH}$, $J = 1$ and 6.5), 2.02 (unresolved quartet, 2 H, CH_2CH_3 , $J = 7$), 4.47 (q, 1 H, $J = 7$, $\text{CH}_3\text{CH}=\text{C}$). IR spectrum (liquid film) cm^{-1} : 1678, 1250, and 835. The isomeric purity was 96–99.5% of *Z* isomer as determined by the submitters by GLC comparison with an authentic *E*-^{6,7} or *Z*-enriched⁷ mixture. The GLC analysis was carried out using the following column and conditions: 3-mm \times 6-m stainless steel column, 5% XE-60 on 60–80 mesh Chromosorb P(AW), 80°C , 45 mL of nitrogen per min. The retention times for the *E*-isomer, the *Z*-isomer, 3-pentanone, and ethyl trimethylsilylacetate are 5.2, 5.6, 6.2, and 15.9 min, respectively.

3. Discussion

Enol trimethylsilyl ethers belong to a most important class of enol derivatives,⁸ and serve as good precursors of isomerically pure enolate anions.^{7,9} The double bond also resembles that of electron-rich olefins in reactions with electrophiles, and sometimes is reactive in electrocyclic reactions.

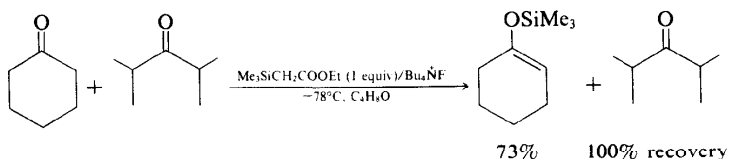
Among the methods for their preparations, two reactions described by House have been employed widely:⁷ a thermodynamically controlled silylation with chlorotrimethylsilane/triethylamine in hot dimethylformamide or a kinetically controlled reaction which involves lithiation with a lithium dialkylamide followed by quenching with the chlorosilane. Each method has its own merits and drawbacks with respect to three important factors: regio-, stereo-, and chemoselectivities.

The present silylation reaction^{10a,b} represents a new procedure based on metathetical generation of reactive enolate species,¹¹ and some characteristic features described below make this reaction complementary to the previous methods.

The excellent stereoselectivity as described in the present example is

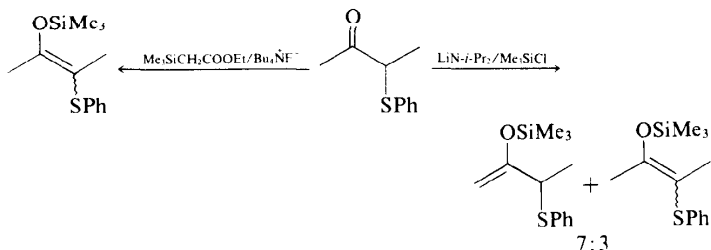
one of the advantages that merits attention.^{10b} The reaction affords only *Z*-enol silyl ethers when applied to acyclic ketones. For instance, silylation of 5-nonanone and 2-octanone gave (*Z*)-5-trimethylsiloxy-4-nonene and (*Z*)-2-trimethylsiloxy-2-octene (together with 14% of its regio isomer), both in 91% yield.

Chemoselectivity of the reaction constitutes another point of interest. Ketones can be silylated in the presence of functional groups which include oxiranes, esters, nitriles,^{10a} and even ketones. Thus silylation of one ketone can be performed in the presence of another. The equation shown below illustrates this selectivity.¹²



Alkyl halides¹¹ and aldehydes¹³ are not compatible with the present silylation reaction.

Kinetic selectivity of the silylation reaction is high with methyl isopropyl ketone (99.5% of the less highly substituted isomer),¹² and methyl isobutyl ketone (~90%), and fair with 2-methylcyclohexanone (~80%).^{10a} The nature of the regioselectivity of this reaction appears different from that with lithium dialkylamide for which steric factors may influence the regioselectivity. In fact, silylation of 3-phenylthio-2-butanone with ethyl trimethylsilylacetate at 0°C produced 2-phenylthio-3-trimethylsiloxy-2-butene, whereas treatment with lithium diisopropylamide followed by quenching with chlorotrimethylsilane gave mainly the less highly substituted regio isomer.¹²



Since the only by-product of the reaction is ethyl acetate, the silylated product can be employed for further reactions without purification. Examples include the fluoride-catalyzed aldol reaction¹⁴ and bromination with *N*-bromosuccinimide.^{10a}

The present reaction can be applied to a variety of ketones including four- to eight-membered and twelve-membered cycloalkanones and acyclic and α,β -unsaturated ketones.^{10a} It has also been used for primary, secondary, and tertiary alcohols,¹⁵ alkanethiols,¹⁵ phenols,¹⁵ and arylacetylenes.^{10a}

Ethyl trimethylsilylacetate has also been used for the synthesis of α,β -unsaturated esters.¹⁶ The chemistry of tetrabutylammonium fluoride as a base with mild reactivity has been reviewed.¹⁷

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(*Z*)-3-Trimethylsiloxy-2-pentene: Silane, [(1-ethyl-1-propenyl)oxy]trimethyl-, (*Z*)-(9); (51425-54-8)

Ethyl trimethylsilylacetate: Acetic acid, (trimethylsilyl)-, ethyl ester (8, 9); (4071-88-9)

Zinc (8, 9); (7440-66-6)

Cuprous chloride: Copper chloride (8); Copper chloride (CuCl) (9); (7758-89-6)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8, 9); (75-77-4)

Ethyl bromoacetate: Acetic acid, bromo-, ethyl ester (8, 9); (105-36-2)

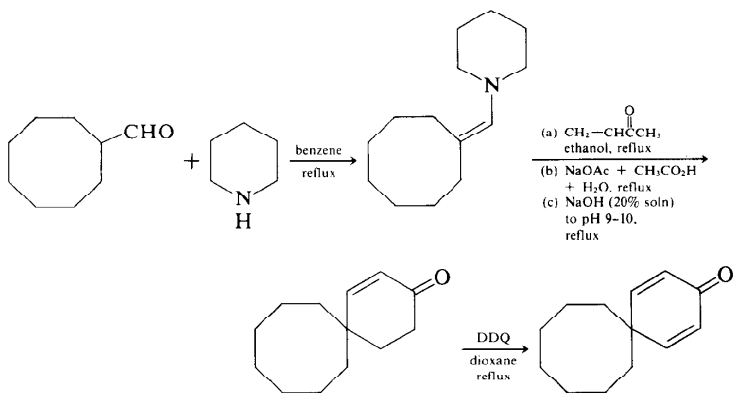
Tetrabutylammonium fluoride hydrate: Ammonium, tetrabutyl-, fluoride, hydrate (8); (22206-57-1)

3-Pentanone (8, 9); (96-22-0)

Tetrabutylammonium hydroxide: Ammonium, tetrabutyl-, hydroxide (8);

1-Butanaminium, *N,N,N*-tributyl-, hydroxide (9); (2052-49-5)

SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE



Submitted by VINAYAK V. KANE and MAITLAND JONES, JR.¹

Checked by R. V. STEVENS and R. P. POLNIASZEK

1. Procedure

Caution! The following reactions should be performed in an efficient hood to protect the experimentalist from noxious vapors (piperidine and methyl vinyl ketone).

A. *1-(Cyclooctylidenemethyl)piperidine*. Cyclooctanecarboxaldehyde (12.5 g, 0.089 mol) (Note 1) and piperidine (8.35 g, 0.098 mol) are dissolved in 115 mL of toluene and placed in a 250-mL, one-necked flask equipped with a magnetic stirring bar and Dean-Stark water separator on top of which is a condenser fitted with a nitrogen inlet tube. The reaction mixture is placed under a nitrogen atmosphere, then brought to and maintained at reflux with stirring for 6 hr, at which time the theoretical amount of water (1.75 mL) has been collected. The reaction mixture is cooled and fractionally distilled under reduced pressure (Note 2): toluene and excess piperidine are removed at 40°C (0.5 mm), and the enamine product is distilled as a colorless liquid to yield 17.30 g (0.084 mol, 93.6%) of 1-(cyclooctylidenemethyl)piperidine, bp 81–83°C (0.5 mm).

B. *Spiro[5.7]tridec-1-en-3-one*. A dry, 1-L, three-necked flask is equipped with a Teflon stirring bar, condenser, pressure-equalizing dropping funnel, and nitrogen inlet tube. To this flask are introduced absolute ethanol (460 mL) (Note 3) and 1-(cyclooctylidenemethyl)piperidine (17.3 g, 0.084 mol). After the solution has been stirred for 5 min, methyl vinyl ketone (6.44 g, 0.092 mol) (Note 4) is added dropwise over a period of 5 min. The solution is refluxed for 20 hr using a heating mantle. The mixture is cooled and anhydrous sodium acetate (15.0 g), acetic acid (25.5 mL), and water (46 mL) are added. The mixture is brought to and maintained at reflux for 8 hr. The heat is removed and the solution is cooled with ice water; aqueous sodium hydroxide (20% solution, approximately 65 mL) is added until pH 9–10 is attained. The solution is refluxed for another 15 hr; at the end of this period the reaction mixture is cooled. The reaction mixture (600 mL) is divided equally into two 2-L separatory funnels and each portion is diluted with 600 mL of ice-cold water. Each separatory funnel is extracted with ether (3 × 125 mL). The ether extract is washed successively with aqueous 5% hydrochloric acid (125 mL) and saturated brine (3 × 170 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent is removed on a rotary evaporator and the product is distilled under vacuum (Note 5) as a colorless liquid to yield 7.05–7.75 g (44–49%) of spiro[5.7]tridec-1-en-3-one, bp 95–125°C (0.5 mm) (Note 6).

C. *Spiro[5.7]trideca-1,4-dien-3-one*. Spiro[5.7]tridec-1-en-3-one (3.63 g, 0.0189 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (8.90 g, 0.0392 mol) (Note 7) are dissolved in 50 mL of dioxane

(Note 8) in a 250-mL, one-necked flask equipped with a magnetic stirring bar fitted with a condenser and drying tube. The reaction mixture is brought to and maintained at reflux with stirring for 6 hr. The mixture is cooled, filtered, and the dioxane removed in a rotary evaporator. The product is taken up in ether (125 mL), and the ether layer is washed with aqueous sodium hydroxide (15%, 4×60 mL). The combined aqueous layers are further extracted with ether (3×60 mL). The ether layers are combined and washed with saturated sodium chloride (4×60 mL), dried over anhydrous magnesium sulfate and filtered. The solvent is removed on the rotary evaporator to afford a crude yellow liquid. To this crude product are added silica gel (6.25 g) (Note 9) and enough ether to cover the silica gel. The ether is removed with a rotary evaporator so as to absorb the crude product on the silica gel. This silica gel dry powder is poured onto a column (12 in. long \times 1.0 in. diameter) containing silica gel (50 g) in hexane. The column is eluted with hexane (70 mL) and then with an increasing amount of ethyl acetate/hexane (Note 10). The desired fractions are combined (Note 11) and solvent is removed under reduced pressure to afford spiro[5.7]trideca-1,4-dien-3-one (2.65 g, 73.7%), (Note 12).

2. Notes

The checkers performed all reactions on $\frac{1}{4}$ the scale reported by the submitters.

1. Cyclooctanecarboxaldehyde was obtained from Aldrich Chemical Company, Inc., and used without purification.

2. 1-(Cyclooctylidenemethyl)piperidine is typical of most enamines in that it discolours rapidly when exposed to air and therefore must be handled under an inert atmosphere, preferably nitrogen.

3. Absolute ethanol, distilled and stored over molecular sieves, was used.

4. Methyl vinyl ketone (bp 35–36°C at 140 mm) was obtained from Aldrich Chemical Company, Inc. and distilled immediately before use.

5. A heating mantle was used for this distillation. A fore-run of 25–95°C (0.5 mm) was discarded. The exact boiling point of spiro[5.7]trideca-1-en-3-one is 86°C (0.1 mm).

6. The product has the following spectral properties: ^1H NMR (CCl_4)

δ : 1.62 (s, 14 H), 1.85 (br d, 2 H), 2.25 (m, 2 H), 5.68 (d, 1 H, $J = 10$ Hz), 6.75 (d, 1 H, $J = 10$ Hz).

7. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, supplied by Aldrich Chemical Company, Inc., was used without further purification.

8. Dioxane was refluxed over potassium hydroxide pellets, distilled, and stored over molecular sieves.

9. Silica gel analytical reagent (60–200 mesh) was obtained from the J. T. Baker Chemical Co.

10. The silica gel column was eluted starting with hexane (70 mL), followed by 2% ethyl acetate/hexane (100 mL); 5% ethyl acetate/hexane (100 mL); 10% ethyl acetate/hexane (600 mL). The fractions were monitored with 20% ethyl acetate/hexane, using silicon 7 GF plates (purchased from Analtech, Inc.), thickness 250 μm , 20 cm long \times 5 cm wide. The plates were sprayed with 3% ceric sulfate and heated at 350°C to detect dienone and monoenone. Alternatively, silica gel 60 F-254 plates (purchased from EM Laboratories, Inc.), thickness 25 mm, 20 cm long \times 5 cm wide may be used. Detection may be made with ultraviolet light. The ratio of 1 g of crude dienone to 15 g of silica gel is adequate for obtaining pure spiro[5.7]trideca-1,4-dien-3-one.

11. When 20% ethyl acetate/hexane is used, the monoenone, R_f 0.57, and the dienone, R_f 0.47 (Analtech Uniplate — Silica 7 GF), are obtained.

12. The product has the following spectral properties: ^1H NMR (CCl_4) δ : 1.65 (s, 14 H), 6.10 (d, 2 H, $J = 10$ Hz), 6.98 (d, 2 H, $J = 10$ Hz).

3. Discussion

This procedure illustrates a general method for preparing a wide range of spirocyclohexenones and hence spirocyclohexadienones. A number of intramolecular and intermolecular reactions are known to give spirodienones; however, these methods have limited synthetic application.² This procedure is superior⁴ to that developed by Bordwell and Wellman,⁴ for side reactions such as aldol condensation of the aldehyde and polymerization of methyl vinyl ketone are avoided. These spirodienones are useful intermediates in the synthesis of paracyclophanes.^{5,6}

Cyclopentanecarboxaldehyde (47%), cyclohexanecarboxaldehyde (41%), 1,2,5,6-tetrahydrobenzaldehyde (43%), cycloheptanecarboxaldehyde (41%), cyclooctanecarboxaldehyde (42%), cycloundecanecarboxaldehyde (36%), 5-norbornene-2-carboxaldehyde (32%), adamantanecarbox-

aldehyde (20%), and 1,2,3,4-tetrahydro-1-naphthylaldehyde (40%) gave corresponding spiroenones.⁷ Spiroenones obtained from cyclohexanecarboxaldehyde, cycloheptanecarboxaldehyde and cyclooctanecarboxaldehyde were converted to the corresponding dienones using the dichlorodicyanobenzoquinone (DDQ). The yields for all three dienones are in the range of 56 to 58%.

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7. Yields are for the overall conversion.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Spiro[5.7]trideca-1,4-dien-3-one (8, 9); (41138-71-0)

Cyclooctanecarboxaldehyde (8, 9); (6688-11-5)

Spiro[5.7]tridec-1-en-3-one (9); (60033-39-8)

Piperidine (8, 9); (110-89-4)

Methyl vinyl ketone: 3-Buten-2-one (8, 9); (78-94-4)

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone [DDQ]: 1,4-Cyclohexadiene-1,2-dicarbonitrile, 4,5-dichloro-3,6-dioxo- (8, 9); (84-58-2)

Cyclopentanecarboxaldehyde (8, 9); (872-53-7)

Cyclohexanecarboxaldehyde (8, 9); (2043-61-0)

1,2,5,6-Tetrahydrobenzaldehyde: 3-Cyclohexene-1-carboxaldehyde (8, 9); (100-50-5)

Cycloheptanecarboxaldehyde (8, 9); (4277-29-6)

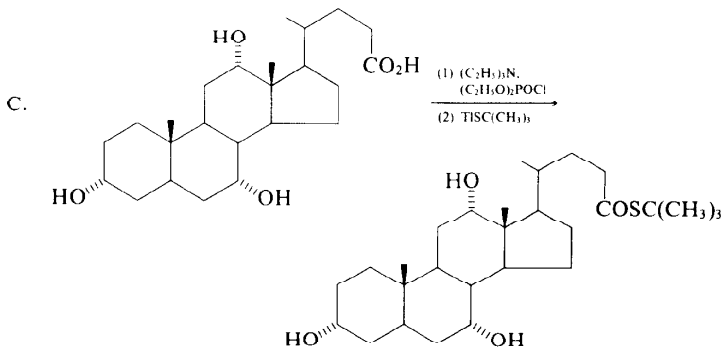
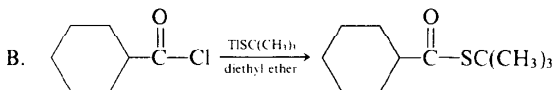
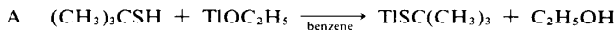
Cycloundecanecarboxaldehyde (9); (4373-07-3)

5-Norbornene-2-carboxaldehyde (8); (5453-80-5)

Adamantanecarboxaldehyde: 1-Adamantanecarboxaldehyde (8); Tricyclo[3.3.1.1^{5,7}]decane-1-carboxaldehyde (9); (2094-74-8)

1,2,3,4-Tetrahydro-1-naphthylaldehyde: 1-Naphthaldehyde, 1,2,3,4-tetrahydro- (8); 1-Naphthalenecarboxaldehyde, 1,2,3,4-tetrahydro- (9); (18278-24-50)

**PREPARATION OF THIOL ESTERS:
THE 2-METHYLPROPANE-2-THIOL ESTERS OF
CYCLOHEXANECARBOXYLIC ACID AND CHOLIC ACID**



Submitted by GARY O. SPESSARD,¹ WAN KIT CHAN,² and S. MASAMUNE²
Checked by TRINA KITTREDGE and ROBERT V. STEVENS

1. Procedure

*Caution! Thallium compounds are very toxic. However, they may be safely handled if prudent laboratory practices are followed. Rubber gloves and laboratory coats should be worn, and reactions should be carried out in an efficient hood. Thallium wastes should be collected and disposed of separately.*³

A. *Thallium(I) 2-methylpropane-2-thiolate.* A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel to which a nitrogen inlet adapter is attached is charged with 47.2 g (0.189 mol) of thallium(I) ethoxide (Note 1) and 200 mL of anhydrous benzene (Note 2). Over a period of 15 min 19.2 g (24 mL, 0.213 mol) of 2-methylpropane-2-thiol (Note 1) is added. The

reaction mixture is stirred under a nitrogen atmosphere for 1 hr and the resulting precipitate is collected by filtration. After washing with three 100-mL portions of anhydrous pentane (Note 3), 48.5–51.2 g (90–95%) of the product is obtained as bright yellow crystals, mp 165–170°C dec (Note 4). This material is sufficiently pure for use in the following steps.

B. S-tert-Butyl cyclohexylmethanethioate. A solution of 4.38 g (0.030 mol) of cyclohexanecarboxylic acid chloride (Note 5) in 150 mL of ether (Note 6) is placed in a dry, 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a gas inlet. The system is flushed with nitrogen and the solution is cooled in an ice bath. Stirring is initiated and 8.82 g (0.031 mol) of the thallium(I) 2-methylpropane-2-thiolate prepared in Step A is added. After the resulting milky suspension is stirred for 2 hr at room temperature, the fine precipitate is removed by filtration through Celite (Note 7) and washed thoroughly with four 50-mL portions of ether. The combined filtrate and washings are concentrated on a rotary evaporator to give a pale yellow oil which is distilled under reduced pressure through a 5-cm Vigreux column. After separation of a forerun, 5.36–5.44 g (90–91%) of the colorless thiol ester is collected, bp 100°C (7 mm) (Note 8).

C. S-tert-Butyl ester from cholic acid. A dry, 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and a nitrogen inlet adapter; the system is purged with, and maintained under, dry nitrogen. After 4.90 g (0.0120 mol) of cholic acid (Note 9), 1.33 g (0.0131 mol) of triethylamine (Note 10), and 60 mL of dry tetrahydrofuran (THF, Note 11) are placed in the flask, a stoppered, pressure-equalizing dropping funnel charged with a solution of 2.18 g (0.0127 mol) of diethyl phosphorochloridate (Note 9) in 30 mL of dry THF is attached to the top of the nitrogen inlet adaptor (see Figure 1). The solution is added to the stirred reaction mixture over a period of 5 min and stirring is continued for 3.5 hr at room temperature. The dropping funnel is removed, and the reaction mixture is taken up into a dry, 100-mL syringe and transferred to a dry filtering apparatus. This apparatus is shown in Figure 2. The glass-fritted filter funnel of medium porosity with a built-in vacuum adapter is connected to the middle neck of a 500-mL, three-necked, round-bottomed flask. A calcium chloride drying tube is connected to the vacuum adapter and a nitrogen inlet adapter is attached to the top of the filter funnel. The precipitated triethylamine hydrochloride is now removed from the reaction mixture by stoppering the nitrogen inlet adapter and using the positive nitrogen pressure to force the solution through the glass frit.

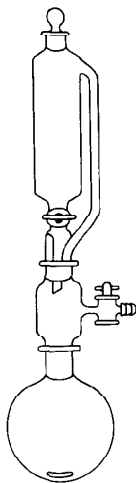


Figure 1

Dry tetrahydrofuran, 40 mL, is used to rinse the original reaction flask. The stopper of the nitrogen inlet adapter (Figure 2) is removed and this washing is transferred via the same syringe to the filtering apparatus and forced through the filter in the same manner described above. One of the stoppers of the three-necked flask is replaced by a nitrogen inlet adapter and the filter funnel is replaced by a mechanical stirrer. As the filtrate is stirred at room temperature, the remaining stopper is removed and 3.90 g (0.0133 mol) of thallium(I) 2-methylpropane-2-thiolate is added. After the addition is complete, the neck is restoppered, and the resulting mixture is vigorously stirred under nitrogen at room temperature overnight. The precipitate is removed by suction filtration through Celite filter aid (Note 7) and washed with three 30-mL portions of THF. The filtrate and washings are combined and concentrated under reduced pressure, and the resulting residue is dissolved in 160 mL of ethyl acetate. This solution is washed with two 100-mL portions of aqueous 5% NaHCO_3 , then with 50 mL of aqueous saturated NaCl , and finally is dried over anhydrous Na_2SO_4 . The solvent is removed by rotary evaporator to afford a white, gummy paste which crystallizes upon trituration with 20 mL of acetonitrile. The crystals are collected by suction filtration to afford 4.2 g of

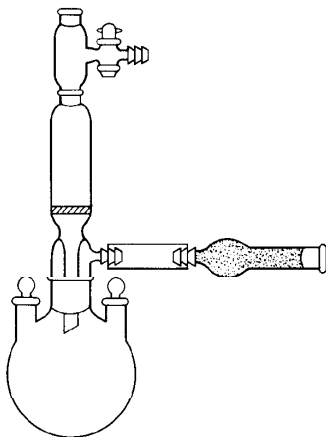


Figure 2

crude product. Recrystallization from 90 mL of hot acetonitrile provides 3.5 g of the thiol ester as small white needles, mp 166–167°C (Note 12). A second crop of 0.5 g, mp 165–166°C, can be obtained upon concentration of the mother liquor to approximately 30 mL, for a combined yield of 70%.

2. Notes

1. Thallium(I) ethoxide and 2-methylpropane-2-thiol were purchased from Aldrich Chemical Company, Inc.

2. Benzene, reagent grade, was purified and dried by first removing the benzene–water azeotrope by simple distillation and then collecting the remaining liquid under an atmosphere of nitrogen.

3. Dry pentane was obtained by allowing practical grade pentane to be shaken with and then distilled from concentrated sulfuric acid.

4. The product should be stored in a dark bottle under an atmosphere of argon to prevent discoloration and possible decomposition.

5. Cyclohexanecarboxylic acid chloride may be prepared in the following way: a pressure-equalizing addition funnel fitted with a nitrogen inlet tube is attached to a 500-mL, round-bottomed flask which is equipped

with a magnetic stirring bar and also charged with 12.8 g (0.100 mol) of cyclohexanecarboxylic acid (purchased from Aldrich Chemical Company, Inc.) and 250 mL of anhydrous ether. (Anhydrous benzene may also be used.) The ethereal solution is cooled to ice bath temperature and 25.4 g (0.200 mol) of oxalyl chloride (purchased from Aldrich Chemical Company, Inc.) is added over a period of 20 min. Under nitrogen, the resulting solution is stirred for 26 hr before it is concentrated on a rotary evaporator to afford a pale yellow oil. Distillation of the oil yields 13.5 g (92%) of cyclohexanecarboxylic acid chloride as a clear, colorless liquid, bp 75°C (30 mm); IR (liquid film) cm^{-1} : 1800 (strong).

6. Anhydrous ether was obtained from Mallinckrodt Inc. and used without further purification.

7. Celite (C-211), purchased from Fisher Scientific Company, was washed thoroughly with ether.

8. The spectral characteristics of the product are as follows: IR (liquid film) cm^{-1} : 1675 (strong); ^1H NMR (neat) δ : 1.42 [s, 9 H, $\text{C}(\text{CH}_3)_3$], 1.0–2.0 (m, 10 H, all CH_2 in cyclohexane portion), 2.3 (m, 1 H, CH).

9. Cholic acid and diethyl phosphorochloridate were obtained from Aldrich Chemical Company, Inc.

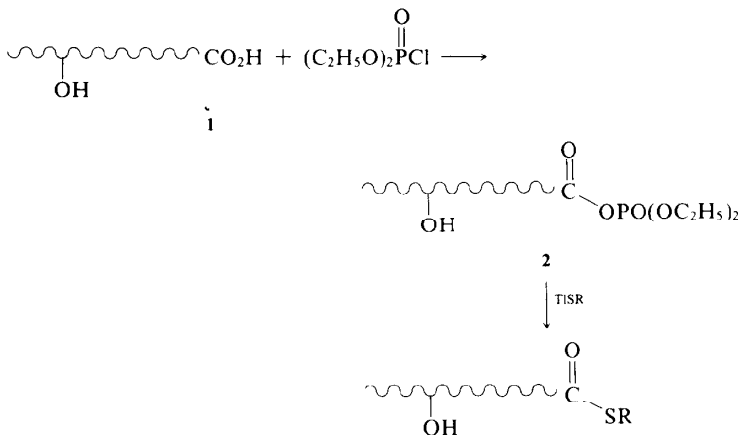
10. Triethylamine was purchased from Eastman Organic Chemicals.

11. Tetrahydrofuran, reagent grade, was refluxed over and distilled from lithium aluminum hydride immediately prior to use.

12. The spectral properties of the product are as follows: IR (CHCl_3) cm^{-1} : 3600 (sharp, weak), 3430 (broad, medium), 1675 (strong), no absorption at 1700.

3. Discussion

Methods available before 1971 for the preparation of thiol esters are briefly summarized in a review article.⁴ Since then, several newer techniques have been developed, to meet a certain set of criteria required for recent synthetic operations. This development may be summarized as follows. Whenever an acid chloride is available, the reaction of the $\text{Ti}(\text{I})$ salt of a thiolate of virtually any kind, including alkane-, benzene-, 2-benzothiazoline-, and 2-pyridinethiol, proceeds efficiently and near-quantitatively. However, if selective thiol ester formation in the presence of hydroxy or other functional groups in the same molecule is required, three main procedures are available. First, reaction of an acid (1), with



a dialkyl or diphenyl phosphorochloridate affords the anhydride (2) (with the hydroxy groups intact) which is subsequently converted to the thiol ester.⁵ This method can be applied to any type of thiol and a variety of hydroxy acids (except for β -hydroxy acids⁶). A mixed anhydride method using ethyl chloroformate and pyridine also effects selective thiol ester formation in many cases.⁷ Secondly, the imidazolidine of an acid which is prepared from 1 and *N,N*-carbonyldiimidazole reacts efficiently with relatively acidic thiols such as benzenethiol to yield the thiol ester.^{6,8} Thirdly, use of a disulfide and triphenylphosphine effects the selective formation of thiol esters, but this technique is only applicable to relatively reactive disulfides such as those derived from 2-benzothiazole-, 2-pyridinethiol,^{9,10} and 4-*tert*-butyl-*N*-isopropylimidazole-2-thiol.¹¹

Other methods that can be used to prepare thiol esters from carboxylic acids include the use of aryl thiocyanates,¹² thiopyridyl chloroformate,¹³ 2-fluoro-*N*-methylpyridinium tosylate,¹⁴ 1-hydroxybenzotriazole,¹⁵ and boron thiolate.¹⁶ Direct conversion of *O*-esters to *S*-esters can also be effected via aluminum and boron reagents.¹⁷ However, the applicability of these¹²⁻¹⁷ and other more recent methods¹⁸ to the selective thiol ester formation discussed above has not been clearly defined.

Thiol esters have recently been utilized, with and without activation, for the preparation of *O*-esters for lactones, in particular, in macrolide syntheses. The accompanying procedure illustrates this conversion.¹⁹

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2. Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2. The present address of S. Masamune is the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Thallium(I) 2-methylpropane-2-thiolate: 2-Propanethiol, 2-methyl-, thallium(I) salt (10); (56393-79-4)

Thallium(I) ethoxide: Ethanol, thallium (1+) salt (8, 9); (20398-06-5)

2-Methylpropane-2-thiol: 2-Propanethiol, 2-methyl- (8, 9); (75-66-1)

S-*tert*-Butyl cyclohexylmethanethioate: Cyclohexanecarbothioic acid, *S* (1,1-dimethylethyl) ester (9); (54829-37-7)

Cyclohexanecarboxylic acid (8, 9); (98-89-5)

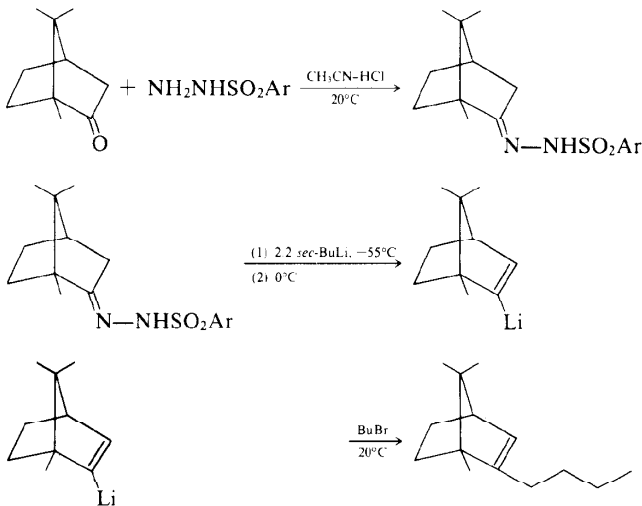
Oxalyl chloride (8); Ethanediol dichloride (9); (79-37-8)

S-*tert*-Butyl ester of cholic acid: Cholane-24-thioic acid, 3,7,12 trihydroxy-*S*-(1,1-dimethylethyl) ester, (3 α ,5 β ,7 α ,12 α)- (9); (58587-05-6)

Cholic acid (8); Cholan-24-oic acid, 3,7,12-trihydroxy-, (3 α ,5 β ,7 α ,12 α) (9); (81-25-4)

Diethyl phosphorochloridate: Phosphorochloridic acid, diethyl ester (8, 9); (814-49-3)

GENERATION AND REACTIONS OF VINYL LITHIUM REAGENTS: SYNTHESIS OF 2-BUTYLBORNENE



Submitted by A. RICHARD CHAMBERLIN, ELLEN L. LIOTTA, and F. THOMAS BOND[†]
Checked by HIROKO MASAMUNE and ROBERT V. STEVENS

1. Procedure

A. *d*-Camphor 2,4,6-triisopropylbenzenesulfonylhydrazone. In a 500-ml. Erlenmeyer flask equipped with a magnetic stirring bar is placed 66.0 g (0.22 mol) of 2,4,6-triisopropylbenzenesulfonylhydrazide (Note

1), 30.4 g (0.20 mol) of *d*-camphor (Note 2), 100 mL of freshly distilled acetonitrile, and 20.0 mL (0.24 mol) of concentrated hydrochloric acid. The resulting solution is stirred overnight while a granular solid precipitates. The white crystals are cooled at -10°C for 4 hr and collected by suction filtration, dissolved in 175 mL of dichloromethane, filtered to remove a small amount of insoluble material, and concentrated under reduced pressure on a rotary evaporator to give 60.8–63.4 g (70–73%) of a white solid, mp $196-199^{\circ}\text{C}$ (dec) (Note 3).

B. 2-Butylbornene. A 1-L, three-necked flask is equipped with a 250-mL addition funnel (sealed with a rubber septum), a mechanical stirrer, and a rubber septum. The system is vented (via a hypodermic needle inserted through the addition funnel septum) through a mineral oil bubbler, and the apparatus is flame-dried while it is flushed with pre-purified nitrogen introduced through the septum of the flask. The flask is charged with 40.0 g (0.092 mol) of *d*-camphor 2,4,6-trisopropylbenzenesulfonylhydrazone, resealed, and again flushed with nitrogen. Hexane, 200 mL, (Note 4), and 200 mL of tetramethylethylenediamine (Note 5), are added, and the stirred solution, under an atmosphere of nitrogen, is cooled to approximately -55°C with an ethanol–water(2 : 1)/dry ice bath. Using a Luer-Lok syringe, 158 mL (0.20 mol) of 1.29 *M* *sec*-butyllithium (Note 6) is transferred to the addition funnel. The solution is stirred rapidly and the *sec*-butyllithium added over a period of 15–20 min. The resulting orange solution is stirred for 2 hr, and the cold bath removed. After 20 min the flask is immersed in an ice bath until nitrogen evolution ceases (approximately 10 min).

To this stirred solution of 2-lithiobornene is added, via syringe, 15.2 g (0.11 mol) of butyl bromide (Note 7) over a 1-min period. The ice bath is then removed, and the reaction mixture is stirred at room temperature overnight. The mixture is poured into 500 mL of water. The layers are separated and the aqueous layer extracted with two 100-mL portions of ether. The combined organic extracts are washed with five 200-mL portions of water, one 50-mL portion of 1 *N* hydrochloric acid, and two 200 mL portions of water. The solution is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator at aspirator pressure and room temperature. Distillation of the residual yellow liquid through a 20-cm Vigreux column affords 8.9–9.4 g (50–53%) of product as a colorless liquid, bp $57-59^{\circ}\text{C}$ (0.5 mm), n_{D}^{25} 1.4664, $[\alpha]_{\text{D}}^{25} -10.7^{\circ}$ (*c* MeOH, 0.0747) (Note 8).

2. Notes

1. The submitters used material prepared following a literature procedure.²

2. *d*-Camphor was purchased from Eastman Kodak Co., $[\alpha]_D^{25} + 39.5^\circ$.

3. The ^1H NMR spectrum is as follows: δ : 0.61 (s, 3 H), 0.86 (s, 6 H), 1.26 (overlapping doublets, $J = 6.7, 18$ H), 1.4–2.2 (m, 7 H), 2.90 (septuplet, $J = 7, 1$ H), 4.20 (septuplet, $J = 7, 2$ H), 7.15 (s, 2 H).

4. Matheson, Coleman, and Bell reagent grade hexane was distilled from lithium aluminum hydride.

5. This compound was purchased from Aldrich Chemical Company, Inc., and distilled from lithium aluminum hydride.

6. The *sec*-butyllithium was purchased from Alfa Products, Ventron Corp., and standardized by double titration or diphenylacetic acid titration. Other alkyllithium bases such as butyllithium and methyllithium cannot be substituted for the stronger *sec*-butyllithium since larger amounts of bornylene are formed because of incomplete dianion formation. Careful attention must be paid to stoichiometry in this reaction; failure to do so also results in increasing the amount of bornylene formed.

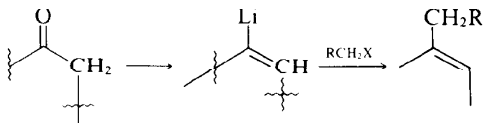
Even under ideal conditions the NMR of crude product shows 20–30% bornylene, which, however, is easily separated from the desired product during distillation as a "forerun" which sublimes into the vacuum pump trap.

7. Analytical reagent material was purchased from Mallinckrodt, Inc., and distilled from calcium hydride.

8. The ^1H NMR spectrum (CDCl_3) is as follows: δ 0.74 (s, 3 H), 0.76 (s, 3 H), 0.94 (s, 3 H), 0.7–1.0 (broad m, 7 H), 1.4 (m, 4 H), 1.9 (m, 2 H), 2.19 ("t", $J = 4, 1$ H), 5.51 (m, 1 H).

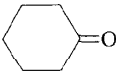
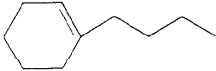
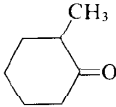
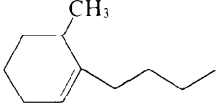
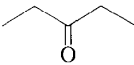
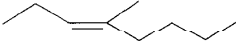
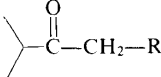
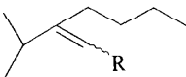
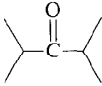
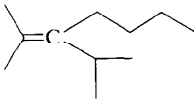
3. Discussion

The sequence described here illustrates a general procedure for converting ketones into alkylated olefins:



It is a modification of the Shapiro olefin synthesis³ which allows the vinyl anion intermediate to be trapped with primary halides and other electrophiles. Use of triisopropylbenzenesulfonylhydrazones as the vinyl lithium precursor⁴ is an improvement over previously⁴ used toluenesulfonylhydrazones,^{5,6} which can be employed in the sequence provided excess *sec*-butyllithium (typically 4.5 equiv) and alkyl halide (3.0 equiv) are used. Methyl ketones (e.g., acetone, acetophenone, 2-octanone) can also be used and can be converted into their dianions using 2.2 equiv of the weaker base, *n*-butyllithium. The conditions described above, with the slight modifications noted, have been used for a variety of ketones as shown in Table I.

TABLE I
KETONE TO BUTYLALKENE CONVERSIONS

Ketone	Product
	 <i>a</i>
	 <i>a,b</i>
	 <i>a</i>
	 <i>a,c</i>
	 <i>d</i>

^a*sec*-Butyllithium is added at -8°C .

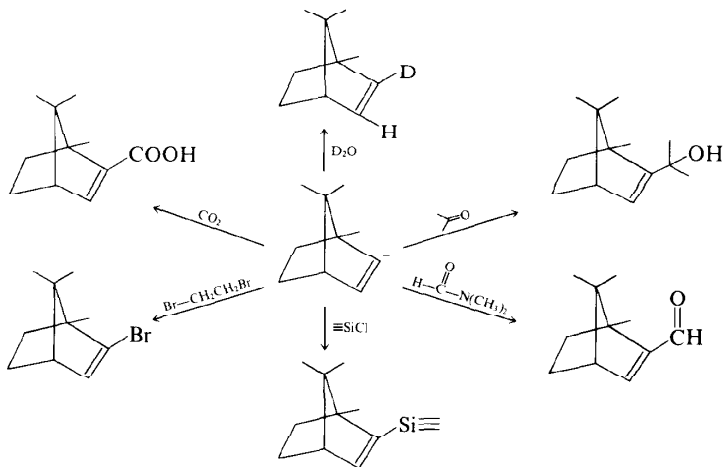
^bApproximately 2% of the isomeric 1-butyl-2-methylcyclohexene is formed.

^cA mixture of (*Z*) and (*E*) isomers is formed.

^dTertiary hydrogen removal is slower. *sec*-Butyllithium (3.0 equiv) is added at -78°C ; the solution is immediately warmed to room temperature and stirred for 1–2 hr before butyl bromide (2.0 equiv) is added.

The submitters have found that the hexane-tetramethylethylenediamine solvent system described above, which is required for toluenesulfonylhydrazones, may be replaced with tetrahydrofuran when triisopropylbenzenesulfonylhydrazones are used, provided that the electrophilic reagent is added to the vinyl lithium species as soon as it is formed (as indicated by cessation of nitrogen evolution).

Primary alkyl bromides react well in this sequence except for particularly reactive compounds (e.g., methyl bromide, allyl bromide) which give the vinyl halide by metal-halogen exchange. Secondary halides, as expected, suffer from elimination as a side reaction. Other electrophiles have been used successfully including D_2O , aldehydes and ketones, dimethylformamide,^{4,7} chlorotrimethylsilane,^{4,8} 1,2-dibromoethane,⁴ and



carbon dioxide. Such sequences allow for relatively straightforward preparation of deuterated olefins, allylic alcohols, α,β -unsaturated aldehydes, vinylsilanes, vinyl bromides, and α,β -unsaturated acids. The major advantages of this route to vinyl lithium reagents⁹ lie in the availability of the ketone precursors and the regioselectivity of the Shapiro reaction.^{3,10} There are numerous alternative routes to trisubstituted olefins.¹¹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,4,6-Triisopropylbenzenesulfonylhydrazide: Benzenesulfonic acid, 2,4,6-tris(1-methylethyl)-, hydrazide (9); (39085-59-1)

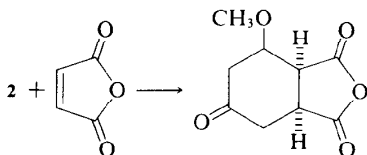
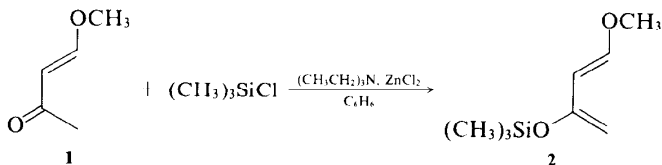
d-Camphor: Camphor (1*R*, 4*R*)-(+) - (8); Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-, (1*R*) - (9); (464-49-3)

Tetramethylethylenediamine: Ethylene, *N,N,N',N'*-tetramethyl- (8); 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl- (9); (110-18-9)

sec-Butyllithium. Lithium, *sec*-butyl- (8); Lithium, (1-methylpropyl)- (9); (598-30-1)

Butyl bromide: Butane, 1-bromo- (8, 9); (109-65-9)

**PREPARATION AND DIELS-ALDER REACTION
OF A HIGHLY NUCLEOPHILIC DIENE:
trans-1-Methoxy-3-trimethylsiloxy-1,3-butadiene
(Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl-)**



Submitted by SAMUEL DANISHEFSKY, TAKESHI KITAHARA, and PAUL F. SCHUDA¹
Checked by DENNIS GOLOB, JOHN DYNAK, and ROBERT V. STEVENS

1. Procedure

A. Preparation of the zinc chloride. Reagent grade zinc chloride (50 g) is placed in an evaporating dish and heated in a fume hood with a Fisher burner until no more water vapor is driven off. The hot dish is rapidly transferred to a glove bag which has been maintained under nitrogen. After the zinc chloride has cooled to a transparent glassy solid, it is ground to a fine powder with a mortar and pestle. The solid is transferred to a tightly stoppered bottle and stored in a desiccator over Drierite.

B. Preparation of 1-methoxy-3-trimethylsiloxy-1,3-butadiene. Triethylamine (575 g, 5.7 mol) is stirred mechanically in a three-necked flask (Note 1). To it is added 10.0 g (0.07 mol) of zinc chloride prepared as described above. The mixture is stirred at room temperature under nitrogen for 1 hr. A solution of 250 g (2.50 mol) of 4-methoxy-3-buten-

2-one (from Aldrich Chemical Company, Inc.) in 750 mL of benzene is added all at once. Mechanical stirring is continued for 5 min. Chlorotrimethylsilane (542 g, 5.0 mol) is added rapidly. The reaction mixture first turns pink, then red, and finally brown. Heat is evolved and the reaction is kept below 45°C by cooling in an ice bath. After 30 min, the mechanically stirred solution is heated by a heating mantle to 43°C (Note 2). This temperature is maintained for 12 hr. The reaction mixture becomes very thick during this time. After the mixture cools to ambient temperature, it is poured, with mixing, into 5 L of ether. The solid material is filtered through Celite. The Celite and solid material are removed and stirred with 4 L more of ether and refiltered through Celite. The combined ether washings are evaporated under reduced pressure (rotary evaporator) to a brown, sweet-smelling oil. The oil is transferred to a 1-L, single-necked flask equipped with an 18-in. Vigreux column (Note 3). Careful fractional distillation under water vacuum affords a forerun of approximately 16 g which boils at 70–78°C (22 mm). This fraction consists of impure diene which contains 4-methoxy-3-buten-2-one. The main fraction boils at 78–81°C (23 mm) and consists of 245 g of diene (Note 4) with approximately 5–10% of 4-methoxy-3-buten-2-one (Note 5). This material is suitable for most purposes. If higher purity is desired, the second fraction may be redistilled under reduced pressure through an 18-in. Vigreux column to afford 200 g (46%) of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Note 6).

C. *5β-Methoxycyclohexan-1-one-3β,4β-dicarboxylic acid anhydride*. To 3.00 g (0.174 mol) of 1-methoxy-3-trimethylsiloxy-1,3-butadiene at 0°C (ice bath) is added a total of 980 mg (0.01 mol) of freshly sublimed maleic anhydride in portions of 70–80 mg each over a period of 25 min. When the addition is complete, the ice bath is removed and the clear solution is stirred for 15 min at room temperature (Note 7). Three 5-mL portions of a solution of tetrahydrofuran (35 mL) and 0.1 N hydrochloric acid (15 mL) are added and the solution is stirred for 1 min. The remaining acid solution (35 mL) is added all at once and the resulting solution is poured into 100 mL of chloroform and treated with 25 mL of water. The organic layer is separated and the aqueous layer is extracted four times with 100-mL portions of chloroform. The extracts are combined and dried over anhydrous magnesium sulfate. The solvent is then removed under reduced pressure (Note 8) to provide 2.0 g of an oil which solidifies. Pentane (10 mL) is added to the oily solid and small portions

of ether (total of 6 mL) are added; trituration is continued until the crystals become free flowing. The crystals are isolated by filtration and washed with 10 mL of 2 : 1 pentane/ether to afford 1.75 g (90%) of the anhydride, mp 87–89°C. Further recrystallization affords an analytically pure sample, mp 97–98°C.

2. Notes

1. The checkers dried all reagents by allowing them to stand over molecular sieves (Type 4A), with the exception of triethylamine, which was dried over potassium hydroxide pellets. The reaction flask was flame-dried. Because of evolution of triethylamine hydrochloride that was encountered during addition of the chlorotrimethylsilane and in the work-up, the reaction should be carried out in a hood.

2. The checkers did not cool the reaction, which allowed the temperature to rise to 55°C. After 30 min, the solution was heated overnight with a heating mantle. After 12 hr, the reaction temperature was 67°C.

3. A 16-in. Widmer column packed with 3-mm glass helices may also be used for the distillation.

4. *Caution! When the temperature begins to drop, heating must be stopped. Otherwise, on occasion, a violent reaction may occur with formation of a gas and rapid expansion of the residual tars.*

5. The checkers performed this distillation at a lower pressure (1–10 mm) through a similar Vigreux column to yield 225 g of clear liquid containing fluffy white material (triethylamine hydrochloride) which could not be removed by filtration. The purity of this distillate, determined by NMR, was 90 : 10 (dien : ketone). No forerun was obtained which contained more than 15% ketone.

6. The checkers carefully redistilled the impure distillate through the same previously mentioned distillation apparatus under water vacuum. Six fractions of various amounts were collected and combined to yield (1) a forerun of 64 g, bp 70–78°C (23–25 mm), purity 77 : 23 (diene : ketone); and (2) 145 g of pure diene, bp 78–81°C (23–25 mm). This second distillation seemed to remove the triethylamine hydrochloride from the product.

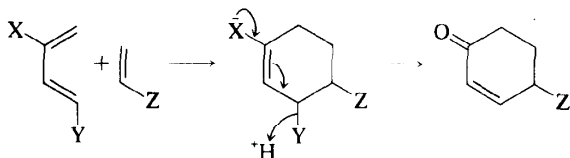
7. The reaction mixture is initially yellow, but turns colorless when the solution is warmed to room temperature.

8. When the chloroform extract is concentrated, care must be exercised to avoid overheating. The temperature should be no greater than 40°C.

3. Discussion

The procedure described here is a scale up of the published method² for the preparation of 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**2**) from readily available reagents. The preparation of this diene has recently been complemented by a report of the preparation of 1,3-bis(trimethylsiloxy)-1,3-butadiene,³ and earlier by a reported synthesis of a 1,3-dialkoxy-1,3-butadiene.⁴

The electron-donating nature of this diene confers high reactivity and orientational specificity in its reaction with unsymmetrical dienophiles.⁵ This fact, coupled with the readily available conversion to the α,β -unsaturated ketone from the imparted functionality, makes 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**2**) a potentially very valuable reagent in organic synthesis. The general reaction scheme is illustrated below:



The high reactivity of the diene is shown by reaction with notoriously unreactive dienophiles such as 1-carbomethoxycyclohexene, 2,5-dihydrobenzoic acid methyl ester,⁶ and 2-methylcyclohex-2-en-1-one to give, after mild work-up, the corresponding α,β -unsaturated ketones in quite respectable yields.⁵

The Diels-Alder reaction with maleic anhydride is illustrative of the high reactivity and potential utility of this diene.

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Appendix**Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)**

trans-1-Methoxy-3-trimethylsiloxy-1,3-butadiene: Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl- (9); 59414-23-2

4-Methoxy-3-buten-2-one: 3-Buten-2-one, 4-methoxy- (8, 9); 4652-27-1

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8, 9); 75-77-4

Maleic anhydride (8); 2,5-Furandione (9); 108-31-6

CUMULATIVE AUTHOR INDEX

FOR VOLUMES 60 AND 61

This index comprises the names of contributors to Volumes **60** and **61** only. For authors to previous volumes, see cumulative indices in Volume **59**, which covers Volumes **55** through **59**, and Volume **54**, which covers Volumes **50** through **54**, and either indices in Collective Volumes **I** through **V** or single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

- Albini, A., **61**, 98
 Anderson, A.G., **60**, 34
- Bach, R.D., **60**, 63
 Balderman, D., **60**, 104
 Barnier, J.P., **60**, 25
 Bastiaansen, L.A.M., **60**, 72
 Bauer, M., **61**, 35
 Berlin, K.D., **61**, 56
 Bettinetti, G.F., **61**, 98
 Blacklock, T.J., **60**, 53
 Böhm, I., **60**, 41
 Bond, F.T., **61**, 141
 Branca, S.J., **61**, 65
 Brown, H.C., **61**, 104
 Buntin, S.A., **61**, 82
- Cassady, J.M., **61**, 77
 Chamberlin, A.R., **61**, 141
 Champion, J., **60**, 18, 25
 Chan, W.K., **61**, 48, 134
 Chang, V.S., **60**, 11
 Chiu, I-C., **61**, 59
 Conia, J.M., **60**, 18, 25
 Crass, G., **61**, 24
 Crossland, I., **60**, 6
- Danishefsky, S., **60**, 66, **61**, 147
 Denis, J.M., **60**, 18
 Dessau, R.M., **61**, 22
- Earl, R.A., **60**, 81
- Farrand, R., **61**, 71
 Fishel, D.L., **61**, 8
 Fleming, M.P., **60**, 113
 Fry, J.L., **60**, 108
- Gassman, P.G., **60**, 14
- Georgiadis, G.M., **61**, 74
 Giesecke, H., **60**, 49
 Godefroi, E.F., **60**, 72
 Gras, J.L., **60**, 88
 Guaciaro, M.A., **61**, 65
 Gunn, B.P., **61**, 59
- Hashimoto, K., **61**, 122
 Heck, R.F., **61**, 82
 Heiba, E.L., **61**, 22
 Herranz, E., **61**, 85, 93
 Hidber, A., **61**, 42
 Hocker, J., **60**, 49
 Hoffman, R. V., **60**, 121
 Höfle, G., **61**, 14
 Hopf, H., **60**, 41
 Howie, G.A., **61**, 77
 Hull, R., **61**, 71
- Ireland, R.E., **61**, 116
- Jones, M. Jr., **61**, 129
- Kalinowski, H.-O., **61**, 24
 Kalir, A., **60**, 104
 Kane, V.V., **61**, 129
 Kitahara, T., **61**, 147
 Kleinschroth, J., **60**, 41
 Knight, J.W., **60**, 63
 Korn, A., **61**, 65
 Kropp, P.J., **61**, 112
 Krumpolc, M., **60**, 20
 Kuwajima, I., **61**, 122
- Lamb, S.E., **60**, 11
 Lange, B., **61**, 14
 Langer, W., **61**, 24
 Lee, D.G., **60**, 11
 Liotta, E.L., **61**, 141

- Little, R.D., **61**, 17
Livinghouse, T., **60**, 126
- McMurry, J.E., **60**, 113
Martin, D., **61**, 35
Masamune, S., **61**, 48, 134
Minoli, G., **61**, 98
Miyashita, M., **60**, 101, 117
- Nakamura, E., **61**, 122
Negishi, E.-I., **61**, 104
Neubert, M.F., **61**, 8
- O'Donnell, D.J., **61**, 56
O'Neil, T.H., **61**, 116
Orfanopoulos, M., **60**, 108
Ottenheijm, H.C.J., **61**, 1
- Padwa, A., **60**, 53
Paquette, L.A., **61**, 39
Peters, R.H., **60**, 92
Pulwer, M.J., **60**, 53
- Ramalingam, K., **61**, 56
Ramarajan, K., **61**, 56
Robinson, J.M., **61**, 77
Roček, J., **60**, 20
Rodewald, P.G., **61**, 22
- Schuda, P.F., **61**, 147
Seebach, D., **61**, 24, 42
Shama, S.A., **61**, 62
Sharpless, K.B., **60**, 29; **61**, 85, 93
- Silverman, S.B., **60**, 108
Singh, R. K., **60**, 66
Skulnick, H.I., **61**, 5
Smith, A.B. III, **61**, 65
Spessard, G.O., **61**, 48, 134
Stamos, I.K., **61**, 77
Stang, P.I., **60**, 34
- Taber, D.F., **61**, 59
Talley, J.J., **60**, 14
Tanabe, M., **60**, 92
Taylor, R. T., **61**, 39
Tijhuis, M.W., **61**, 1
Tise, F.P., **61**, 112
Tolman, G.L., **61**, 116
Townsend, L.B., **60**, 81
- Umbreit, M., **60**, 29
- Van Lier, P.M., **60**, 72
Venegas, M.G., **61**, 17
- Wamser, C.C., **61**, 62
White, D.A., **60**, 1, 58, 78
Wierenga, W., **61**, 5
Wilka, E.-M., **61**, 24
Williams, A.L., **61**, 22
Wilson, S.R., **61**, 74
Wovkulich, P.M., **61**, 65
- Yanami, T., **60**, 101, 117
Yoshikoshi, A., **60**, 101, 117

CUMULATIVE SUBJECT INDEX FOR VOLUMES 60 AND 61

This index comprises subject matter for Volumes 60 and 61 only. For subjects in previous volumes, see the cumulative indices in Volume 59, which covers Volumes 55 through 59, and Volume 54, which covers Volumes 50 through 54, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedure. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in brackets. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

ACETAMIDE, *N*-(2,4-DIFORMYL-5-HYDROXYPHENYL)- [67149-23-9], **60**, 49

Acetamide, *N*-[2,4-bis(1,3-diphenyl 2 imidazolidinyl)-5-hydroxyphenyl]-[67149-22-8], **60**, 50

Acetamide, *N*-(3-hydroxyphenyl)-[621-42-1], **60**, 49

3-Acetamidophenol, **60**, 49

Acetic acid [64-19-7], **61**, 22

Acetic acid, bromo-, ethyl ester [105-36-2], **61**, 122

Acetic acid, diphenyl-, **61**, 42

Acetic acid, manganese(2+) salt, tetrahydrate [6156-78-1], **61**, 22

Acetic acid, (1-methylethenyl) ester, **60**, 67

Acetic acid, palladium(2+) salt [3375-31-3], **61**, 82

Acetic acid, trifluoro-, mercury(2+) salt [13257-51-7], **61**, 48

ACETIC ACID, (TRIMETHYLSILYL)-, ETHYL ESTER [4071-88-9], **61**, 122

Acetic acid-2-¹³C [1563-80-0], drying of, **60**, 97

Acetic acid anhydride [108-24-7], **61**, 22

Acetic anhydride, **61**, 22

Acetone cyanohydrin, **60**, 127

p-Acetylbenzonitrile cyanohydrin, **60**, 17

1-Acetylcyclopropanecarboxylic acid, **60**, 69

ACID CHLORIDES FROM α -KETO ACIDS, **61**, 1

ACRYLIC ACID, 2-(BROMOMETHYL)-, METHYL ESTER, **61**, 77

2-Adamantanone, **60**, 105, 113

ADAMANTYLIDENEADAMANTANE, **60**, 113

Adogen 464 [50934-77-5], **60**, 11

ALIPHATIC β -KETOESTERS, **61**, 5

4-ALKYL CHLORIDES, **61**, 8

Aluminate(1-), tetrahydro-, lithium, [16853-85-3], **61**, 42

Aluminum chloride [7446-70-0], **61**, 8

Amines from tertiary alcohols, table, **60**, 107

m-Aminobenzotrifluoride, **60**, 121

5-Aminotetrazole, **61**, 14

5-Aminotetrazole monohydrate, **61**, 14

Ammonium, benzyltriethyl-, chloride, **61**, 24, 85

Ammonium, tetrabutyl-, fluoride, hydrate [22206-57-1], **61**, 122

Ammonium, tetrabutyl-, hydroxide, **61**, 122

ANDROSTANOLONE, **61**, 116

ANDROSTAN-3-ONE, 17-HYDROXY-, (5 α , 17 β)-[521-18-6] **61**, 116

5 α -ANDROSTAN-3-ONE, 17 β -HYDROXY-, **61**, 116

ANDROST-2-EN-17-OL, (5 α , 17 β)-[2639-53-4], **61**, 116

5 α ANDROST-2-EN-17 β -OL, **61**, 116

Aniline, **60**, 68

o-Anisic acid, **61**, 59

ANODIC OXIDATION OF ACIDS, **60**, 1

AROMATIC β -KETOESTERS, **61**, 5

Arylsulfonyl chlorides, table, **60**, 124

ASYMMETRIC SOLVENT INDUCTIONS,

61, 24

ATROPALDEHYDE, 60, 6

Atropaldehyde diethyl acetal, 60, 7

13-Azabicyclo[7.3.1]tridecan-5-ol,

stereoisomer [61714-12-3], 61, 103

2-Azido-2-phenyladamantane, 60, 104

Benzaldehyde [100-52-7], 61, 42

Benzamidine hydrochloride, 60, 53

Benzenamine, *N*-methyl-, trifluoroacetate
[29885-95-8], 60, 88Benzenamine, 3-(trifluoromethyl)- [98-16-8],
60, 121Benzene, 1,1'-(1-chloro-3-
methylcyclopropane-1,2-diyl)bis-, 60, 56Benzene, (2,2-dichlorocyclopropyl)- [2415-80-
7], 60, 6

Benzene, (2,2-diethoxycyclopropyl)-, 60, 8

Benzene, 1,1'-(1,2-ethenediyl)bis-, (*E*)- [103-
30-0], 61, 85, 93

Benzene, 1-ethyl-3-nitro- [7369-50-8], 60, 108

Benzene, hexamethyl- [87-85-4], 61, 98

Benzene, iodo- [591-50-4], 61, 82

BENZENE, (ISOCYANOMETHYL)- [10340-
91-7], 61, 14BENZENE, 1,1'-(3-METHYL-1-
CYCLOPROPENE-1,2-DIYL)BIS-
[51425-87-7], 60, 53

Benzene, pentyl [538-68-1], 61, 8

Benzene, 1-propenyl-(*E*)- [873-66-5], 60, 54BENZENEACETALDEHYDE, α -
METHYLENE [4432-63-7], 60, 6Benzenecetic acid, α -phenyl [117-34-0], 61,
42BENZENEACETONITRILE, α -
HYDROXY- α -PHENYL [4746-48-9], 60,
14Benzenecarboximidamide monohydrochloride
[1670-14-0], 60, 53Benzenemethanaminium, *N,N,N*-triethyl-,
chloride [56-37-1], 60, 7, 68; 61, 24, 85BENZENEMETHANOL, α -BUTYL- [583-
03-9], 61, 42BENZENEMETHANOL, α -BUTYL-, (*R*)-
[19641-53-3], 61, 42BENZENEPROPANAL, α METHYL [5445
77-2], 61, 82Benzenesulfonamide, *N*-chloro-4-methyl-,
sodium salt, trihydrate [7080-50-4], 61, 85BENZENESULFONAMIDE, *N*-(2-

HYDROXY-CYCLOHEXYL)-4-

METHYL-, *cis*-[58107-40-7], 61, 85Benzenesulfonic acid, 2,4,6-tris(1-
methylethyl)-, hydrazide [39085-59-1], 61,
141BENZENESULFONYL CHLORIDE, 3-
(TRIFLUOROMETHYL)- [777-44-6], 60,
121

Benzoic acid, 60, 13

Benzoic acid, 2-methoxy- [579-75-9], 61, 59

Benzophenone, 60, 15

BENZOPHENONE CYANOHYDRIN, 60,
14*p*-Benzoquinone, 60, 128*p*-Benzoquinone monotrimethylsilyl
cyanohydrin, 60, 126

3,1-BENZOXAZEPINE [15123-59-8], 61, 98

Benzoyl chloride, 60, 73

BENZOYL CHLORIDE, 4-PENTYL- [49763-
65-7], 61, 81-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-
yl)imidazole, 60, 73

Benzyl bromide, 60, 93

BENZYL ISOCYANIDE, 61, 14

4-Benzoyloxy-2-butanone, 60, 93

5-Benzoyloxy-3-hydroxy-3-methylpentanoic
acid-2-¹³C, 60, 94

Benzyltriethylammonium chloride, 61, 24, 85

Bicyclo[7.3.0]dodecane-1,5-diol, 61, 103

Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-,
(1*R*)-[464-49-3], 61, 141BICYCLO[4.1.0]HEPT-3-ENE, 7,7-
DIBROMO-1,6-DIMETHYL- [38749-43
8], 61, 39BICYCLO[2.2.0]HEXA-2,5-DIENE,
1,2,3,4,5,6-HEXAMETHYL [7641-77-2],
61, 622,2'-Bi-1*H*-imidazole, 1,3-dibenzoyl-2,3-
dihydro-, monohydrochloride [65276-00-
8], 60, 742,2'-Bi-1*H*-imidazole, 1,1',3-tribenzoyl-2,3-
dihydro- [62457-77-6] 60, 73

2,2'-Bipyridine [366-18-7], 61, 5, 65

2,2'-Bipyridyl, 61, 5, 65

BIRCH REDUCTION, 61, 59

(S,S(+))-1,4-BIS(DIMETHYLAMINO)-2,3-
DIMETHOXYBUTANE [DDB], 61, 24*N*[2,4-Bis(1,3-Diphenylimidazolidin-2-yl)-5-
hydroxyphenyl] acetamide, 60, 50BIS(2,2,2-TRICHLOROETHYL)
AZODICARBOXYLATE, 61, 17

- 1,2-bis(Trimethylsiloxy)-cyclobutene, **60**, 19
 Borane-tetrahydrofuran, **61**, 103
 9b-BORAPHENALENE,
 DODECAHYDRO-[16664-33-8]; *cis,cis*-:
 (3 $\alpha\alpha$,6 $\alpha\alpha$,9 $\alpha\alpha$), [1130-59-2]; *cis,trans*-:
 (3 $\alpha\alpha$,6 $\alpha\alpha$,9 $\alpha\beta$), [2938-53-6], **61**, 103
 Borate (1-), cyclododecane-1,5,9-triylhydro-,
 lithium, **61**, 103
 Borate (1-), 1,5,9-cyclododecane triylhydro-,
 lithium [36005-35-3], **61**, 103
 Borate(1-), tetrahydro-, sodium [16940-66-2],
 61, 85
 Boric anhydride-sulfuric acid scrubber, **60**,
 110
 Boron trifluoride butyl etherate, **60**, 27
 Boron trifluoride etherate, **61**, 116
 Bromine [7726-95-6], **61**, 35
 2-BROMO-2-CYCLOPENTENONE, **61**, 65
 2-BROMOCYCLOPENTENONE
 ETHYLENE KETAL, **61**, 65
 Bromoform, **61**, 39
 1-Bromoheptane, **61**, 59
 1-Butanaminium, *N,N,N*-tributyl-, perchlorate
 [1923-70-2], **60**, 58
 1-Butanaminium, *N,N,N*-tributyl-, hydroxide
 [2052-49-5], **61**, 122
 Butane, 1-bromo- [109-65-9], **61**, 141
 BUTANEDIAMIDE,2,3-DIHYDROXY-
 N,N,N',N'-TETRAMETHYL-[*R,R,R*]-
 [26549-65-5], **61**, 24
 BUTANEDIAMIDE, 2,3-DIMETHOXY-
 N,N,N',N'-TETRAMETHYL-[*R,R*]-
 [26549-29-1], **61**, 24
 1,4-BUTANEDIAMINE-2,3-DIMETHOXY-
 N,N,N',N'-TETRAMETHYL-, (*S,S*)(+)-,
 61, 42
 Butanedioic acid, 2,3-dihydroxy-[*S,S*]- [147-
 71-7], **61**, 24
 BUTANEMETHANOL, α -BUTYL-, (*S*)-
 [33652-83-4], **61**, 42
 1,2,3,4-BUTANETETRACARBOXYLIC
 ACID, TETRAETHYL ESTER [4373-15-
 3], **60**, 58
 2-Butanone, 4-hydroxy- [590-90-9], **60**, 93
 2-Butanone, 4-phenylmethoxy- [6278-91-7],
 60, 93
 2-Butenedioic acid, (*E*)-, diethyl ester [623-91-
 6], **60**, 58, 59
 2-Butenoic acid, ethyl ester, (*E*)- [623-70-1],
 61, 85
 3-Buten-2-one [78-94-4], **61**, 129
 3-Buten-2-one, 4-methoxy- [4652-27-1], **61**,
 147
tert-Butyl alcohol, **61**, 85
tert-Butyl alcohol, 2-Propanol, 2-methyl- [75-
 65-0], **61**, 116
 2-BUTYLBORNENE, **61**, 141
 Butyl bromide, **61**, 141
S-tert-BUTYL
 CYCLOHEXYLMETHANETHIOATE,
 61, 48, 134
S-tert-BUTYL ESTER OF CHOLIC ACID,
 61, 134
 Butyllithium, **61**, 74, 116
n-Butyllithium, **61**, 5, 42
sec-Butyllithium, **61**, 141
t-Butyl phenyl ketone cyanohydrin, **60**, 17
 2-Butyne [503-17-3] **61**, 62
 2-Butynedioic acid, dimethyl ester [762-42-5],
 60, 69
 2-BUTYNOIC ACID, 4-HYDROXY-,
 METHYL ESTER [31555-05-2], **60**, 81
 3-Butyn-1-ol, **60**, 82
 γ -BUTYROLACTONES, **61**, 22
d-Camphor, **61**, 141
 Carbamic acid, ethyl ester [51-79-6], **61**, 93
 Carbamic acid chloro-, ethyl ester, sodium
 salt [17510-52-0], **61**, 93
 CARBAMIC ACID (2-HYDROXY-1,2-
 DIPHENYLETHYL)-. ETHYL ESTER.
 (*R^**,*R^**)[73197-89-4], **61**, 93
 Carbomethoxylation of Grignard reagent, **60**,
 86
 Carbonochloridic acid, methyl ester [79-22-1],
 60, 83
 Carbonochloridic acid, 2,2,2-trichloroethyl
 ester [17341-93-4], **61**, 17
 Carbonothioic dichloride [463-71-8], **61**,
 71
 Carbon tetrachloride, **61**, 35
 Carbostyryl [493-62-9], **61**, 98
 CARBOXYLIC ACIDS FROM
 OXIDATION OF TERMINAL
 ALKENES, **60**, 11
 CHIRAL MEDIA, **61**, 24
 Chloramine-T trihydrate, **61**, 85
p-Chloroacetophenone cyanohydrin, **60**, 17
N-CHLORO-*N*-
 ARGENTOCARBAMATES, **61**, 93
 (*S*)-1-Chloro-(*S,R*)-1,2-diphenyl-(*S*)- 3-methyl
 cyclopropane, **60**, 56

- (*S*)-1-Chloro-(*S,S*)-1,2-diphenyl-(*R*)-3-methyl cyclopropane, **60**, 56
- 9b-Chlorododecahydro-, *cis,cis,trans*-(3 α ,6 α ,9 α ,9b β) [52079-56-8], **61**, 103
- 9b-chloroperhydrophenalene, **61**, 103
- CHLOROPHENYL CARBENE, **60**, 53
- Chlorotrimethylsilane, **61**, 122, 147
- CHOLANE-24-THIOIC ACID, 3,7,12-TRIHYDROXY-*S*-(1,1-DIMETHYLETHYL) ESTER, (3 α ,5 β ,7 α ,12 α)-[58587-05-6], **61**, 134
- Cholan-24-oic acid, 3,7,12-trihydroxy-, (3 α ,5 β ,7 α ,12 α) [81-25-4], **61**, 134
- Cholic acid, **61**, 134
- Chromatography column, water-jacketed, **60**, 37
- Chromium trioxide, **60**, 21
- Clemmensen reaction, **60**, 111
- Copper chloride (CuCl) [7758-89-6], **61**, 122
- Crotonic acid, ethyl ester, (*E*)-, **61**, 85
- 18-Crown-6-potassium cyanide complex, **60**, 129
- Crum Brown-Walker reaction, **60**, 4
- Cuprous chloride, **60**, 42, 121; **61**, 122
- CYANIC ACID, PHENYL ESTER [1122-85-6], **61**, 35
- CYANIC ACID ESTERS, **61**, 35
- 1-Cyanocyclopropanecarboxylic acid, **60**, 69
- CYANOGEN BROMIDE [506-68-3], **61**, 35
- Cyanohydrins, **60**, 14, 17
- Cyanosilylation, **60**, 15, 126 table, **60**, 131
- 1,2-Cyclobutanediol, *cis* [35358-33-9], **60**, 26
- 1,2-Cyclobutanediol, *trans* [35358-34-0], **60**, 26
- 1,2-CYCLOBUTANEDIONE [33689-28-0], **60**, 18
- Cyclobutanol, **60**, 22
- CYCLOBUTANONE [1191-95-3], **60**, 20
- Cyclododecanone [830-13-7], **61**, 74
- 1,5,9-Cyclododecatrione [4904-61-4], **61**, 103
- CYCLODODECENE [1501-82-2] [(*E*)-1486-75-5, (*Z*)-1129-89-1], **60**, 29
- trans*-CYCLODODECENE, **60**, 29
- trans*-Cyclododecene oxide, **60**, 31
- CYCLODODECYL MERCAPTAN, **61**, 74
- 1,4-Cyclohexadiene, 1,2-dimethyl- [17351-28-9], **61**, 39
- 2,5-Cyclohexadiene-1-carbonitrile, 4-oxo-1-[(trimethylsilyl)oxy]-[40861-57-2], **60**, 126
- 1,4-Cyclohexadiene, 1,2-dicarbonitrile, 4,5-dichloro-3,6-dioxo- [84-58-2], **61**, 129
- 2,5-Cyclohexadiene-1,4-dione [106-51-4], **60**, 128
- CYCLOHEXANE, 1-METHOXY-1-METHYL-4-(1-ETHENYL-1-METHYL)-*cis* [24655-71-8], **61**, 112
- CYCLOHEXANE, 1-METHOXY-1-METHYL-4-(1-ETHENYL-1-METHYL)-, *trans*- [24655-72-9], **61**, 112
- CYCLOHEXANECARBOTHIOIC ACID, *S*-(1,1-DIMETHYLETHYL) ESTER [34829-37-7], **61**, 48, 134
- Cyclohexanecarboxylic acid [98-89-5], **61**, 134
- CYCLOHEXANECARBOXYLIC ACID, *tert*-BUTYL ESTER, **61**, 48
- CYCLOHEXANECARBOXYLIC ACID, 1,1-DIMETHYLETHYL ESTER [16537-05-6], **61**, 48
- Cyclohexane-1,3-dione, **61**, 59
- 1,3-Cyclohexanedione [504-02-9], **61**, 59
- CYCLOHEXANONE, 2-(2-OXOPROPYL)- [6126-53-0], **60**, 117
- Cyclohexanone cyanohydrin, **60**, 17
- Cyclohexene [110-83-8], **61**, 85
- CYCLOHEXENE, 1-METHYL-4-(1-METHYLETHENYL)- [5989-27-5], **61**, 112
- Cyclooctanecarboxaldehyde [6688-11-5], **61**, 129
- Cyclooctanone cyanohydrin, **60**, 17
- Cyclooctene [931-88-4], **61**, 85
- Cyclooctene, (*Z*)- [931-87-3], **60**, 63
- cis*-Cyclooctene, **60**, 63
- cis*-CYCLOOCTENE OXIDE, **60**, 63
- 3a,7(1*H*)-Cyclopentacyclononenediol, decahydro- [52318-91-9], **61**, 103
- 2-Cyclopentenone, **61**, 65
- 2-Cyclopenten-1-one [930-30-3], **61**, 65
- 2-CYCLOPENTEN-1-ONE, 2-BROMO- [10481-34-2], **61**, 65
- CYCLOPROPANECARBOXALDEHYDE [1489-69-6], **60**, 25
- Cyclopropane-1,1-dicarboxylic acid [598-10-7], **60**, 67
- Cyclopropanemethanol [2516-33-8], **60**, 21
- Cyclopropylcarbinol, **60**, 21
- DECANEDIOIC ACID, DIMETHYL ESTER [106-79-6], **60**, 1
- 1-Decene, **60**, 13
- 1-Decene [872-05-9], **61**, 22, 85
- (*Z*)-5-Decene, **61**, 85

- 5-Decene, (*Z*)- [7433-78-5], **61**, 85
- DEOXYGENATION OF EPOXIDES, **60**, 29
- DIAZENEDICARBOXYLIC ACID,
BIS(2,2,2-TRICHLOROETHYL) ESTER
[38857-88-4], **61**, 17
- 3H-Diazirine, 3-chloro-3-phenyl- [4460-46-2],
60, 55
- Diazotization, **60**, 121
- 2-(1,3-Dibenzoylimidazolidin-2-yl)-imidazole
hydrochloride, **60**, 74
- 2-(1,3-Dibenzoyl-4-imidazolin-2-yl)-imidazole
hydrochloride, **60**, 74
- 7,7-DIBROMO-1,6-DIMETHYLBICYCLO[4.1.0]HEPT-3-
ENE, **61**, 39
- 1,2-Dibromoethane, **60**, 67
- β,β'*-Dibromoisobutyric acid, **61**, 77
- 2,6-Di-*t*-butyl-4-methylpyridine, **60**, 34
recovery of, **60**, 39
- 2,6-Di-*t*-butyl-4-methylpyrylium
trifluoromethanesulfonate, **60**, 34
- 2,6-Di-*t*-butyl-4-neopentylpyridine, **60**, 37
- 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
[DDQ], **61**, 129
- α,α -Dichloromethyl methyl ether, **61**, 1
- 1,1-Dichloro-2-phenylcyclopropane, **60**, 6
- DIELS-ADLER REACTION, **61**, 147
OF 1,2,4,5-HEXATETRAENE, **60**, 41
- DIETHYL BIS(HYDROXYMETHYL)-
MALONATE, **61**, 56
- Diethyl bis(hydroxymethyl)malonate, **61**, 77
- Diethyl ethoxysuccinate, **60**, 59
- Diethyl fumarate, **60**, 58, 59
- Diethyl maleate, **60**, 59
- Diethyl malonate, **60**, 67
- Diethyl phosphorochloridate, **61**, 134
- Diethyl succinate, **60**, 59
- Diethyl tartrate, **61**, 24
- N*-(2,4-DIFORMYL-5-HYDROXYPHENYL)ACETAMIDE,
60, 49
- Diglyme, **61**, 103
- Dihydropyran, **60**, 82
- Diisopropylamine, **61**, 116
- 1,4-Diketones, table, **60**, 120
- Dimethoxyethane purification, **60**, 115
- 2,3-DIMETHOXY-*N,N,N',N'*-
TETRAMETHYL-*[S,S]*[26549-21-3], **61**,
24
- (*R,R*)-(+)-2,3-DIMETHOXY-*N,N,N',N'*-
TETRAMETHYLSUCCINIC ACID
- DIAMIDE, **61**, 24
- Dimethyl acetylenedicarboxylate, **60**, 43
- Dimethylamine, **61**, 24, 116
- 1,2-Dimethyl-1,4-cyclohexadiene, **61**, 39
- DIMETHYL DECANEDIOATE, **60**, 1
- 6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-
dione, **60**, 67
- Dimethyl hexanedioate, **60**, 2
- N,N*-Dimethylphosphoramidic dichloride, **61**,
116
- Dimethyl 1,3-propanedioate, **60**, 78
- Dimethyl sulfate, **61**, 24
- Dimethyl tetradecanedioate, **60**, 4
- 1,6-DIMETHYLTRICYCLO[4.1.0.0.
2.7]HEPT-3-ENE, **61**, 39
- 5,7-Dioxaspiro[2.5]octane-4,8-dione. 6,6-
dimethyl- [5617-70-9], **60**, 67
- Diphenylacetic acid, **61**, 42
- 1,2-DIPHENYL-3-METHYLCYCLOPROPENE, **60**, 53
- 1,4-DITHIASPIRO[4.11]HEXADECANE
[16775-67-0], **61**, 74
- 1-Docosene, **60**, 13
- Dowex 50-X4 cation resin, for hydrolysis of
acetals, **60**, 86
- 1-Eicosene [3452-07-1], **60**, 11
- ELECTROHYDRODIMERIZATION, **60**,
58
- electrode assembly for, **60**, 1
- Electrolysis:
pH control in, **60**, 61
power supply for, **60**, 60, 79
- ENAMINES, **61**, 129
- ENTIOSELECTIVE ADDITION, **61**, 42
- EPOXIDATION, **60**, 63
- O*-ESTERS, **61**, 48
- Ethanamine, *N,N*-diethyl- [121-44-8], **61**, 35,
77, 103
- Ethane, 1,2-dibromo- [106-93-4], **60**, 67
- Ethane. 1,1'-oxybis-, compared with
trifluoroborane (1 : 1) [109-63-7], **61**, 116
- 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl-
[110 18 9], **61**, 141
- Ethanedioic acid dihydrate [6153-56-6], **60**,
21
- 1,2-Ethanediol [107-21-1], **61**, 65, 103
- Ethanedioyl dichloride [79-37-8], **61**, 8, 134
- 1,2-Ethanedithiol [540-63-6], **61**, 74
- Ethane, 1,1'-oxybis(2-methoxy)- [111-96-6],
61, 103

- 1,1,2,2-ETHANETETRACARBOXYLIC ACID, TETRAETHYL ESTER, [5464-22-2], **60**, 78
- Ethanol, thallium (1+) salt [20398-06-5], **61**, 134
- Ethanone, 1-(3-nitrophenyl)- [121-89-1], **60**, 109
- Ether, bis(2-methoxyethyl), **61**, 103
- Ether, dichloromethyl methyl, **61**, 1
- ETHER, *p*-MENTH-8-EN-1-YL METHYL, *cis*-, **61**, 112
- ETHER, *p*-MENTH-8-EN-1-YL METHYL, *trans*-, **61**, 112
- Ethyl bromoacetate, **61**, 122
- ETHYL α -(BROMOETHYL)ACRYLATE, **61**, 56
- ETHYL 2-BUTYRYLACETATE, **61**, 5
- Ethyl carbamate, **61**, 93
- Ethyl *N*-chloro-*N*-sodiocarbamate, **61**, 93
- Ethyl crotonate, **61**, 85
- Ethylenediamine, *N,N,N',N'*-tetramethyl-, 1,2-Ethanediamine. *N,N,N',N'*-tetramethyl- [110-18-9], **61**, 116
- Ethylene glycol, **61**, 65, 103
- Ethyl ether, compared with boron fluoride (BF₃) (1 : 1), **61**, 116
- Ethylmagnesium bromide, **60**, 83
- ETHYL *threo*-[1-(2-HYDROXY-1,2-DIPHENYL)ETHYL]CARBAMATE, **61**, 93
- ETHYL THIMETHYLSILYLACETATE, **61**, 122
- Fluorenone cyanohydrin, **60**, 17
- Formic acid, **60**, 7
- Formic acid, chloro-, 2,2,2-trichlorethyl ester, **61**, 17
- Formic acid, methyl ester [107-31-3], **61**, 1
- Formylation of phenols, **60**, 52
- 3-Formylquinoline-2(1H)-thione, **61**, 71
- o*-(2-FORMYLVINYL)PHENYL ESTER, (*E*)-, **61**, 71
- o*-(2-FORMYLVINYL)PHENYL ESTER, (*Z*)- [19908-02-2], **61**, 71
- Furan, tetrahydro-, compared with borane (1 : 1) [14044-65-6], **61**, 103
- 2,5-Furandione [108-31-6], **61**, 147
- 2(3*H*)-FURANONE, DIHYDRO-5-OCTYL- [2305-05-7], **61**, 22
- 4-HALOBENZOYL CHLORIDES, **61**, 8
- Heneicosanoic acid, **60**, 13
- Heptadecanoic acid, **60**, 13
- Heptane, 1-bromo- [629-04-9], **61**, 59
- Heptanoic acid, **60**, 13
- 2-HEPTYL-2-CYCLOHEXENONE, **61**, 59
- 1-Hexadecene, **60**, 13
- Hexamethylbenzene, **61**, 98
- HEXAMETHYL DEWAR BENZENE, **61**, 62
- Hexamethylphosphorotriamide, **61**, 116
- Hexanedioic acid, dimethyl ester [627-93-0], **60**, 2
- Hexanedioic acid, monomethyl ester [627-91-8], **60**, 1
- 1,4,7,10,13,16-Hexaoxacyclooctadecane [17455-13-9], **60**, 129
- 1,2,4,5-HEXATETRAENE [29776-96-3], **60**, 41
- HOMOCONJUGATE ADDITION, **60**, 66
- Homo-Michael acceptor, **60**, 69
- Hydrazine hydrate, **61**, 17
- Hydrazine monohydrate [7803-57-8], **61**, 17
- HYDROCINNAMALDEHYDE, α -METHYL-, **61**, 82
- Hydrogen peroxide-acetonitrile, **60**, 63
- 17 β -HYDROXY-5 α -ANDROST-2-ENE, **61**, 116
- 4-Hydroxy-2-Butanone, **60**, 93
- 2-Hydroxycyclobutanone [17082-63-2], **60**, 27
- 2-HYDROXYMETHYL-2-CYCLOPENTENONE, **61**, 65
- Imidazole, **60**, 73
- IMIDAZOLE-2-CARBOXALDEHYDE, **60**, 72
- 1*H*-IMIDAZOLE-2-CARBOXALDEHYDE [10111-08-7], **60**, 72
- Imidazolidine, 1,3-dibenzo-yl-2-(1*H*-imidazol-2-yl)-, monohydrochloride [65276-01-9], **60**, 74
- Imidazolidine, 2-(1,3-diphenyl-2-imidazolidinyldene)-1,3-diphenyl [2179-89-7], **60**, 50
- Iodobenzene, **61**, 82
- 1,3-Isobenzofurandione [85-44-9], **60**, 101
- Isobutene, **61**, 116
- Isobutryl chloride, **61**, 5
- o*-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE, **61**, 71
- o*-ISOTHIOCYANATO-(*Z*)-CINNAMALDEHYDE, **61**, 71

ISOTHIOCYANIC ACID, **61**, 71Kolbe electrolysis, **60**, 4LIMONENE, **61**, 112Lithium, butyl [109-72-8], **61**, 5, 42, 74, 116Lithium, (1-methylpropyl)- [598-30-1], **61**, 141Lithium aluminum hydride, **61**, 42Lithium cyanide [2408-36-8], **60**, 127Lithium hydride [7580-67-8], **60**, 127Lithium perhydro-9b-boraphenyl hydride,
61, 103Magnesium, **60**, 42Maleic anhydride, **61**, 147

MALONIC ACID,

BIS(HYDROXYMETHYL)-, DIETHYL
ESTER [20605-01-0], **61**, 56Malonic acid, bis(hydroxymethyl)-, diethyl
ester [20605-01-0], **61**, 77Malonic acid, monoethyl ester, **61**, 5Malonic acid, monoethyl ester, potassium
salt, **61**, 5Manganese acetate tetrahydrate, **61**, 22(+)-*p*-MENTHA-1,8-DIENE, **61**, 112*cis-p*-MENTH-8-EN-1-YL METHYL
ETHER, **61**, 112*trans-p*-MENTH-8-EN-1-YL METHYL
ETHER, **61**, 112MERCAPTANS FROM THIOKETALS, **61**,
74Mercury, (aceto-*O*)phenyl- [62-38-4], **61**, 82Mercury, (aceto)phenyl-, **61**, 82Mercury(II) chloride, **60**, 42Mercury oxide [21908-53-2], **61**, 48Mercury(II) oxide, red, **61**, 48Mercury(II) trifluoroacetate, **61**, 48Methanamine, *N*-methyl- [124-40-3], **61**, 24,
116Methane, dichloromethoxy- [4885-02-3], **61**,
1Methane, tetrachloro- [56-23-5], **61**, 35Methane, tribromo- [75-25-2], **61**, 39Methanone, diphenyl- [119-61-9], **60**, 14*p*-Methoxyacetophenone cyanohydrin, **60**, 174-Methoxy-3-buten-2-one, **61**, 147*5β* METHOXYCYCLOHEXAN-1-ONE-
3 β ,4 β -DICARBOXYLIC ACID
ANHYDRIDE, **61**, 147

-1-METHOXY-3-

TRIMETHYLSILOXY-1,3-

BUTADIENE, **61**, 147*p*-Methylacetophenone cyanohydrin, **60**, 17*N*-Methylanilinium trifluoroacetate, **60**, 88METHYL α -(BROMOMETHYL)ACRYLATE, **61**, 77Methyl chloroformate, **60**, 83Methyl β , β' -dibromoisobutyrate, **61**, 77 α -METHYLENE KETONES AND
ALDEHYDES, **60**, 88

2-METHYLENE-1-OXO-1,2,3,4-

TETRAHYDRONAPHTHALENE, **60**,
88Methylene transfer, **60**, 90Methyl formate, **61**, 1Methyl hydrogen hexanedioate, **60**, 1METHYL 4-HYDROXY-2-BUTYNOATE,
60, 81Methyl lithium [917-54-4], **61**, 392-Methyl-2-Pentene, **61**, 852-METHYL-3-PHENYLPROPANAL, **61**,
822-Methylpropane-2-thiol, **61**, 1342-Methyl-2-propen-1-ol, **61**, 82*trans-β*-Methylstyrene, **60**, 54Methyl vinyl ketone, **61**, 129(R,S)-MEVALONOLACTONE-2-¹³C, **60**, 92Monoethyl malonate, **61**, 51(2*H*)-Naphthalenone, 3,4-dihydro- [529-34-
0], **60**, 881(2*H*)-NAPHTHALENONE, 3,4-
DIHYDRO-2-METHYLENE- [13203-73-
1], **60**, 88Nitric acid, fuming, **61**, 17*m*-Nitroacetophenone, **60**, 109*p*-Nitroacetophenone cyanohydrin, **60**, 17*m*-NITROETHYLBENZENE, **60**, 108Nitroolefins, **60**, 1032-Nitro-1-propanol, **60**, 102preparation, **60**, 1022-NITROPROPENE, **60**, 101, 118NONADECANOIC ACID [646-30-0], **60**, 11Nonanoic acid, **60**, 131-Octadecene, **60**, 131-Octene, **60**, 13 γ -(*n*-OCTYL)- γ -BUTYROLACTONE, **61**,
22

Organic peroxides:

removal, **60**, 64test for, **60**, 64

- Osmium oxide, **61**, 85
 Osmium oxide, (*T*)-[20816-12-0], **61**, 85
 Osmium tetroxide, **61**, 85
 9-OXABICYCLO[6.1.0]NONANE, *cis*-[4925-71-7], **60**, 63
trans-13-Oxabicyclo[10.1.0]tridecane [4683-60-7], **60**, 31
 Oxalic acid dihydrate, **60**, 21
 Oxalyl chloride, **61**, 8, 134
 1,3-OXAZEPINES, **61**, 98
 OXIDATION OF 5-AMINOTETRAZOLES, **61**, 14
 2-OXO-1-PHENYL-3-PYRROLIDINECARBOXYLIC ACID, **60**, 66
 2-(2-OXOPROPYL)CYCLOHEXANONE, **60**, 17
 Palladium acetate, **61**, 82
 Paracyclophanes, table, **60**, 47
 Paraformaldehyde [30525-89-4], **61**, 65
 Paraformaldehyde (polyoxymethylene), **60**, 88
 Pentadecanoic acid, **60**, 13
 PENTANOIC-2-¹³C ACID, 3-HYDROXY-3-METHYL-5-(PHENYLMETHOXY)-[57830-65-6], **60**, 94
 PENTANOIC ACID, 4-METHYL-3-OXO-, ETHYL ESTER [7152-15-0], **61**, 5
 3-Pentanone [96-22-0], **61**, 122
 2-Pentene, 2-methyl- [625-27-4], **61**, 85
 4-PENTYLBENZOYL CHLORIDE, **61**, 8
 Perhydro-9b-azaphenylene, **61**, 103
 PERHYDRO-9b-BORAPHENYLENE, **61**, 103
 Perhydrophenylene, **61**, 103
 PERHYDRO-9b-PHENALENOL, **61**, 103
 2-(PERHYDRO-9'b-PHENALYL)-1,3,2-DIOXABOROLE, **61**, 103
 Phase transfer alkylation, **60**, 67
 Phase transfer oxidation, **60**, 13
 1*H* Phenalene, **61**, 103
 Phenalene, 9b α -chloro-2,3,3a α ,4,5,6,6a α ,7,8,9,9a β ,9b-dodecahydro [33343-40-7], **61**, 103
 1*H*-Phenalene, dodecahydro- [2935-07-1], **61**, 103
 1*H*-Phenalene, dodecahydro-, (3a α ,6a α ,9a α ,9b β) [40250-64-4], **61**, 103
 PHENALENE-9b(2*H*)-BORONIC ACID, DECAHYDRO-, CYCLIC ETHYLENE ESTER [18604-57-4], **61**, 103
 PHENALENE-9b α (2*H*)-OL, 3,3a α ,4,5,6,6a α ,7,8,9,9a β -DECAHYDRO-[16664-34-9], **61**, 103
 PHENALENE-9b(2*H*)-OL, DECAHYDRO-*cis,cis,trans*-, **61**, 103
 Phenol [108-95-2], **61**, 35
 Phenol aldehydes, table, **60**, 51
 Phenols, **61**, 35
 2-Phenyl-2-adamantanamine, **60**, 105
 2-PHENYL-2-ADAMANTANAMINE HYDROCHLORIDE, **60**, 104
 2-Phenyl-2-adamantanol, **60**, 105
 Phenylchlorodiazirine, **60**, 55
 PHENYL CYANATE, **61**, 35
 1-Phenyl-2,2-diethoxycyclopropane, **60**, 8
 Phenylmercuric acetate, **61**, 82
 1-PHENYL-1-PENTANOL, **61**, 42
 (+)-(*R*)-1-PHENYL-1-PENTANOL, **61**, 42
 (*S*)-1-PHENYL-1-PENTANOL, **61**, 42
N-Phenylpyrrolidinone, **60**, 68
 Phosphoramidic dichloride, dimethyl- [677-43-0], **61**, 116
 Phosphoric triamide, hexamethyl- [680-31-9], **61**, 116
 Phosphorochloridic acid, diethyl ester [814-49-3], **61**, 134
 Phosphorodiamidic chloride, tetramethyl- [1605-65-8], **61**, 116
 Phosphorus oxide [1314-56-3], **61**, 35, 42, 116
 Phosphorus oxychloride [POCl₃], **61**, 116
 Phosphorus pentoxide, **61**, 42, 116
 Phosphoryl chloride [10025-87-3], **61**, 116
 PHOTOISOMERIZATION OF HETEROAROMATIC *N*-OXIDES, **61**, 98
 PHOTOPROTONATION OF CYCLOALKENES, **61**, 112
 Phthalic anhydride, **60**, 101
 Piperidine [110-89-4], **61**, 129
 Pivaloyl chloride, **60**, 35
 Potassium monoethylmalonate, **61**, 5
 Potassium permanganate [7722-64-7], **61**, 22
 2-Propanamine, *N*-(1-methylethyl)- [108-18-9], **61**, 116
 Propanedioic acid, diethyl ester [105-53-3], **60**, 67
 Propanedioic acid, diethyl ester, ion(1-), sodium [996-82-7], **61**, 71
 Propanedioic acid, dimethyl ester [108-59-8], **60**, 78

- Propanedioic acid, monoethyl ester [1071-46-1], **61**, 5
- Propanedioic acid, monoethyl ester, potassium salt [6148-64-7], **61**, 5
- Propanenitrile, 2-hydroxy-2-methyl- [75-86-5], **60**, 127
- 2-Propanethiol, 2-methyl- [75-66-1], **61**, 134
- 2-Propanethiol, 2-methyl-, thallium(I) salt [56392-79-4], **61**, 134
- Propanoic acid, 3-bromo-2-(bromomethyl)- [41459-42-1], **61**, 77
- Propanoic acid, 2-oxo- [127-17-3], **61**, 1
- 2-Propanol, 2-methyl [75-65-0], **61**, 85
- 1-Propanol, 2-nitro- [2902-96-7], **60**, 102
- Propanoyl chloride, 2,2-dimethyl- [3282-30-2], **60**, 35
- Propanoyl chloride, 2 methyl [79-30-1], **61**, 5
- PROPANOYL CHLORIDE, 2-OXO- [5704-66-5], **61**, 1
- Propargyl alcohol, **60**, 82
- Propargyl bromide, **60**, 42
- 1-Propene, 3,3-diethoxy-2-phenyl-, **60**, 7
- 1-Propene, 2-methyl- [115-11-7], **61**, 116
- 1-PROPENE, 2-NITRO- [4789-28-4], **60**, 101, 118
- 2-PROPENOIC ACID, 2-(BROMOMETHYL)-, ETHYL [17435-72-2], **61**, 56
- 2-PROPENOIC ACID, 2-(BROMOETHYL)-, METHYL ESTER [4224-69-5], **61**, 77
- 2-Propen-1-ol, 2-methyl- [513-42-8], **61**, 82
- 2-PROPENYL, 3-(2-ISOTHIOCYANATOPHENYL)-, (*E*)- [19908-01-1], **61**, 71
- Propionic acid, 3-bromo-2-(bromomethyl)-, methyl ester [22262-60-8], **61**, 77
- 1-Propyne, 3-bromo- [106-96-7], **60**, 42
- 2-Propyn-1-ol [107-19-7], **60**, 82
- 2H-Pyran, 3,4-dihydro- [110-87-2], **60**, 82
- 2H-Pyran, tetrahydro-2-(2-propynyloxy)- [6089-04-9], **60**, 82
- 2H-Pyran-2-one-3-¹³C, tetrahydro-4-hydroxy-4-methyl- [53771-22-5], **60**, 92
- PYRIDINE, 2,6-BIS(1,1-DIMETHYLETHYL)-3-METHYL- [38222-83-2], **60**, 34
- Pyrido(2,1,6-*de*)quinolizine, dodecahydro-*cis,cis*-(3 α ,6 α ,9 α) [57147-57-6]; *cis,trans*-(3 α ,6 α ,9 β) [57194-67-9], **61**, 103
- PYRROLIDINECARBOXYLIC ACID, 2-OXO-1-PHENYL- [56137-52-1], **60**, 66
- Pyruvic acid, **61**, 1
- PYRUVOYL CHLORIDE, **61**, 1
- Quinoline [91-22-5], **61**, 71
- 3-Quinolinedicarboxaldehyde, 1,2-dihydro-2-thioxo- [51925-41-8], **61**, 71
- Quinoline 1-oxide [1612-37-2], **61**, 98
- Quinoline *N*-oxide, **61**, 98
- 2(1*H*)-Quinolinone [59-31-4], **61**, 98
- REDUCTION OF KETONES, **60**, 108
- REDUCTIVE ALKYLATION, **61**, 59
- REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES, **61**, 116
- REDUCTIVE COUPLING, **60**, 113
- table, **60**, 116
- Silane, chlorotrimethyl- [75-77-4], **60**, 127; **61**, 122, 147
- Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl][17082-61-0], **60**, 19
- Silane, (1-cyclohexen-1-yloxy)trimethyl- [6651-36-1], **60**, 118
- SILANE, [(1-ETHYL-1-PROPYNYLOXY)TRIMETHYL-, (*Z*)- [51425-54-8], **61**, 122
- SILANE, [(3-METHOXY-1-METHYLENE-2-PROPENYL)OXY]TRIMETHYL- [59414-23-2], **61**, 147
- Silane, triethyl- [617-86-7], **60**, 109
- Silane carbonitrile, trimethyl- [7677-24-9], **60**, 15, 126
- Silver oxide, **60**, 95
- SILYLATION OF KETONES, **61**, 122
- Silyl enol ethers, **60**, 117
- Sodio diethyl malonate, **61**, 71
- Sodium borohydride, **61**, 85
- Sodium cyanide [143-33-9], **61**, 35
- Sodium hypobromite, **61**, 14
- Spiroacylals, **60**, 69
- SPIRO[5.7]TRIDECA-1,4-DIEN-3-ONE [41138-71-0], **61**, 129
- SPIRO[5.7]TRIDEC-1-EN-3-ONE [60033-39-8], **61**, 129
- Stilbene, (*E*)-, **61**, 85
- (*E*)-Stilbene, **61**, 93
- Styrene, **60**, 7, 13
- α -formation of, **60**, 10

SUCCINAMIDE, 2,3-DIMETHOXY-

N,N,N',N'-TETRAMETHYL-(+)-, **61**,

24

Sulfuric acid, dimethyl ester [77-78-1], **61**, 24(R,R)-(+)-Tartaric acid, **61**, 24(S,S)-(-)-Tartaric acid, **61**, 24(+) -Tartaric acid [87-69-4], **61**, 24Tartaric acid, diethyl ester, **61**, 24(R)-(+)-Tartaric acid, diethyl ester, (+)-[608-84-4], **61**, 24(R,R)-(+)-Tartaric acid, diethyl ester, **61**, 24TARTRAMIDE, *N,N,N',N'*-TETRAMETHYL-(+)-, **61**, 24Tetrabutylammonium fluoride hydrate, **61**, 122Tetrabutylammonium hydroxide, **61**, 122Tetrabutylammonium perchlorate, **60**, 581-Tetradecene, **60**, 13

TETRAETHYL 1,2,3,4-

BUTANETETRACARBOXYLATE, **60**, 58Tetrahydro-2-(2-propynyloxy)-2H-pyran, **60**, 82 α -Tetralone, **60**, 88*N,N,N',N'*-Tetramethyldiamidophosphorochloridate, **61**, 116(S,S)-(+)-*N,N,N',N'*-TETRAMETHYL-1,4-DIAMINO-2,3-DIMETHOXYBUTANE [DDB], **61**, 42

TETRAMETHYL 1,1,2,2-

ETHANETETRACARBOXYLATE, **60**, 78Tetramethylethylenediamine, **61**, 141*N,N,N',N'*-Tetramethylethylenediamine, **61**, 116TETRAMETHYL[2.2]PARACYCLOPHANE-4,5,12,13-TETRACARBOXYLATE, **60**, 41(R,R)-(+)-*N,N,N',N'*-TETRAMETHYLTARTARIC ACID DIAMIDE, **61**, 241,1',3,3'-Tetraphenyl-2,2'-biimidazolidinylidene, **60**, 501*H*-Tetrazol-5-amine [4418-61-5], **61**, 141*H*-TETRAZOL-5-AMINE, *N*-(PHENYLMETHYL)-[14832-58-7], **61**, 141*H*-Tetrazole, 5-amino, **61**, 141*H*-Tetrazole, 5-amino-, monohydrate [15454-54-3], **61**, 141*H*-TETRAZOLE, 5-(BENZYLAMINO)-, **61**, 14Thallium(I) ethoxide, **61**, 134Thallium(I) 2-methylpropane-2-thiolate, **61**, 134THIOL ESTERS, **61**, 48preparation of, **61**, 134Thiophosgene, **61**, 71Titanium chloride [7705-07-9], **60**, 113Titanium trichloride, **60**, 113*p*-Toluenesulfonamide, *N*-chloro-, sodium salt, **61**, 85*cis*-2-(*p*-TOLUENESULFONAMIDO)CYCLOHEXANOL, **61**, 852,2,2-Trichloroethyl chloroformate, **61**, 17Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl-, **60**, 105TRICYCLO[3.3.1.1^{3,7}]DECAN-2-AMINE, 2-PHENYL-, HYDROCHLORIDE, **60**, 104Tricyclo[3.3.1.1^{3,7}]decan-2-azido-2-phenyl-[65218-96-4], **60**, 104TRICYCLO[3.3.1.1^{3,7}]DECANE, TRICYCLO[3.3.1.1^{3,7}]DECYLIDENE-[30541-56-1], **60**, 113Tricyclo[3.3.1.1^{3,7}]decan-2-ol, 2-phenyl-[29480-18-0], **60**, 105Tricyclo[3.3.1.1^{3,7}]decanone [700-58-3], **60**, 105, 113TRICYCLO[8.2.2.2^{4,7}]HEXADECA-4,6,10,12,13,15-HEXAENE-5,6,11,12-TETRACARBOXYLIC ACID, TETRAMETHYL ESTER [37437-90-4], **60**, 41Tridecanoic acid, **60**, 13Triethylamine, **61**, 35, 77, 103Triethylbenzylammonium chloride, **60**, 7, 68Triethylsilane, **60**, 109*m*-TRIFLUOROMETHYL-BENZENESULFONYL CHLORIDE, **60**, 121 α,α,α -Trifluoro-*m*-toluidine, **60**, 1212,4,6-Triisopropylbenzenesulfonylhydrazide, **61**, 141Trimethylchlorosilane, **60**, 127(Z)-3-TRIMETHYLSILOXY-2-PENTENE, **61**, 122O-(Trimethylsilyl)benzophenone cyanohydrin, **60**, 15TRIMETHYLSILYL CYANIDE, **60**, 15, 126

1-Trimethylsilyloxycyclohexene, **60**, 118
Tungsten chloride [*13283-01-7*], **60**, 30
Tungsten hexachloride, **60**, 30

VICINAL OXYAMINATION OF
OLEFINS, **61**, 85, 93
VINYLLITHIUM REAGENTS,

GENERATION AND REACTIONS OF,
61, 141

Wolff-Kishner reaction, **60**, 111

Zinc [*7440-66-6*], **61**, 122

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METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

VOLUME 62

1984

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* begin a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure, and to make the annual volumes more easily available to users. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Division of the American Chemical Society. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60-64 will be included in a new five-year version of the collective volumes of *Organic Syntheses* which will appear as *Collective Volume Seven* in the traditional hard cover format, after the appearance of annual volume 64. It will be available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendices. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is adopted. For example, both diethyl ether and ethyl ether are normally used. Since ethyl ether is the established *Chemical Abstracts* name for the 8th Collective Index, it has been used in this volume. The 9th Collective Index name is 1,1'-oxybisethane, which the Editors consider too cumbersome.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds that are of general interest, as well as procedures that illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should be checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yield should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point range should be reported, and for each liquid product the boiling-point range and refractive index should be included. In most instances it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, mass, or nuclear magnetic resonance spectra, and criteria of purity such as gas chromatographic data. In the event that any of the reactants are not commercially available at reasonable cost, their preparation should be described in as complete detail and in the same manner as the prep-

aration of the product of major interest. The sources of the reactants should be described in the Notes section, and physical properties such as boiling point, index of refraction, and melting point of the reactants should be included except where standard commercial grades are specified.

Beginning with Volume 49, Methods of Preparation (Sec. 3) and Merits of the Preparation (Sec. 4) have been combined into Discussion (Sec. 3). This section should include descriptions of related and practical methods. Other published methods that have no practical synthetic value do not need to be mentioned. Those features of the procedure that recommend it for publication in *Organic Syntheses* should be cited (synthetic method of considerable scope, specific compound of interest not likely to be made available commercially, method that gives better yield or is less laborious than other methods, etc.). If possible, a brief discussion of the scope and limitations of the procedure as applied to other examples, as well as a comparison of the particular method with the other methods cited, should be included. If necessary to the understanding or use of the method for related syntheses, a brief discussion of the mechanism may be placed in this section. The present emphasis of *Organic Syntheses* is on model procedures rather than on specific compounds (although the latter are still welcomed), and the Discussion should be written to help readers decide on the value of the procedure in their research. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. An accompanying letter setting forth the features of the preparations that are of interest or value is helpful to the Board.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary.

JOHN R. JOHNSON

August 9, 1900–May 25, 1983

John Raven Johnson, known as Jack Johnson to all his friends, was a member of the first Board of Directors of *Organic Syntheses* when it was incorporated in the state of New York, December 11, 1939. He continued membership for about 20 years. Prior to this, Jack served for about 8 years on the Active Board of Editors, soliciting preparations and checking them. He was Editor-in-Chief of two annual volumes, Vol. XVI (1936) and Vol. XIX (1939). He also served on the Advisory Board of Editors until his death.

Jack Johnson was born in Chicago, August 9, 1900. He attended Lincoln School, Lane Technical High School and Lane Junior College and entered the University of Illinois (Urbana) in 1917. He received a B.S. in Chemistry in 1919; an M.S. in 1920 and the Ph.D. in 1922 just prior to his 22nd birthday. His Ph.D. research and thesis were carried out under the direction of Roger Adams. He received an American Field Fellowship for study abroad and spent two years at the College de France, working with Charles Maureau and Charles Dufraisse, two outstanding French organic chemists. Jack learned many new laboratory techniques, which he taught his research students and colleagues on his return to the states.

From 1924 to 1927, Jack Johnson served as instructor in organic chemistry at the University of Illinois (Urbana). Besides teaching and directing research problems for seniors and graduate students he collaborated with Roger Adams in publishing *Elementary Laboratory Experiments in Organic Chemistry*. It was first published in 1928 and had many revisions. This book, now in its 7th edition, has been edited in recent years by Charles F. Wilcox, one of Johnson's colleagues at Cornell University; *Adams and Johnson* was as well known in the U.S.A. as the classic *Gatterman-Wieland*.

In 1927, Jack Johnson became assistant professor at Cornell University thus starting a career which extended almost 40 years at that school. He restructured the courses in organic chemistry and developed a broad program of research. His enthusiasm and personal contributions led to his promotion to full professor in 1930 when he was barely 30 years old.

He was elected to the National Academy of Science in 1948 and was appointed to the endowed Todd Professorship at Cornell in 1952, a position he held until his retirement in 1965. In addition to his service on the Editorial Boards of

Organic Syntheses and *Organic Reactions*, Jack and his students published research papers on organo-boron compounds, furan derivatives, dienes, ketene derivatives, the structure of gliotoxin, and biosynthesis of isoprene derivatives.

As an outgrowth of an advanced Organic Chemistry course which Jack developed at Cornell, he prepared a 117 page chapter on *Modern Electronic Concepts of Valence*, which was published in Gilman's *Advanced Treatise on Organic Chemistry*, Volume II, 1938.

Jack was a consultant to the research division of duPont from 1937 to 1967 and encouraged the development of the great advances in polymer chemistry by Carothers, a friend from his Illinois days, and his co-workers at duPont.

During the period 1941–1945, Jack served on the NDRC and OSRD research projects connected with the war effort. He, with his collaborators at Cornell, contributed to the anti-malarial program and was a consultant to the penicillin program. He was a co-author with H. T. Clark and Sir Robert Robinson of the monograph *The Chemistry of Penicillin*. This volume summarized the work in the British and American Laboratories. In 1951 Jack served for a year in West Germany as special consultant to the U.S. State Department. For his wartime services he received the U.S. Medal of Merit and the *Medaille d'Honneur* of France. After his war service, Jack again took up his teaching and research at Cornell until he retired in 1965. A special symposium was held at Cornell in May of 1965 in honor of Jack Johnson's achievements.

Shortly after Jack moved to Cornell, he met Hope Anderson, A.B. Mt. Holyoke, 1923. They were married in 1929 and had a happy home, raising two sons, Keith and Leonard, in spite of the depression and war years. After retirement in 1965 Hope and Jack moved to their farm in Deer Valley, Townshend, Vermont. They enjoyed gardening and travel on passenger-carrying freighters to many parts of the world. In recent years, Jack developed emphysema and this ultimately led to his death on May 28, 1983. Jack Johnson played an important role in the growth of organic chemistry from 1922 to 1965. His many friends, students and colleagues remember him and honor him for his achievements.

PREFACE

This annual volume continues the recent style of *Organic Syntheses* with emphasis on modern synthesis methodology. There are 28 checked procedures.

The first seven procedures are examples of metal-promoted processes and reflect the growing importance of organo-transition metal intermediates in organic synthesis. The synthesis of **Z-1-IODOHEXENE** demonstrates the copper-promoted carbo-metalation of acetylene starting from organo-lithium reagents, with high specificity in the geometry of the alkene. Extension of the Wacker process to a general conversion of terminal alkenes into methyl ketones is exemplified by the formation of **2-DECANONE**. The use of organocuprates is shown again through the conjugate addition-elimination reaction of enol phosphates of β -ketoesters to produce a **β -METHYL- α,β -UNSATURATED CARBOXYLIC ACID ESTER**. The value of lead(IV) compounds in activating electron-rich aromatic rings toward coupling with carbon nucleophiles is shown by the conversion of anisole directly to the *p* (triacetoxylead) derivative and then coupling with a β -ketoester in pyridine, resulting in overall arylation of the β -ketoester. The coupling of main group organo metal species with organic halides catalyzed by Pd(O) is one of the most powerful and general techniques for carbon-carbon bond formation. Included here are the coupling of a vinyl-alane with an allylic chloride to produce **α -FARNESENE** and the coupling of an aryl-lithium with *cis*- β -bromostyrene to give a ***cis*-1,2-DIARYLETHYLENE**. Both processes show the impressive selectivities characteristic of the general method. Nucleophilic addition to alkenes catalyzed by Pd(II) shows up again in the intramolecular addition of a sulfonamide to a mono-substituted alkene, producing a **DIHYDROPYRROLE** derivative. This sequence also demonstrates the conversion of a secondary hydroxyl to an amino group with inversion using diethyl azodicarboxylate and triphenylphosphine.

Seven procedures describe preparation of important synthesis intermediates. A two step procedure gives **2-(HYDROXYMETHYL)ALLYLTRIMETHYLSILANE**, a versatile bifunctional reagent. As the acetate, it can be converted to a trimethylenemethane-palladium complex (*in situ*) which undergoes [3 + 2] annulation reactions with electron-deficient alkenes. A preparation of halide-free **METHYLLITHIUM** is included because the presence of lithium halide in the reagent sometimes complicates the analysis and use of methyllithium. Commercial samples invariably contain a full molar equivalent of bromide or iodide. **AZULENE** is a fundamental compound in organic chemistry; the preparation

described in this volume is efficient and can be applied to substituted versions. The dienophile, **3-ACETYL-2(3H)-OXAZOLONE**, is an attractive intermediate for the synthesis of vicinal aminoalcohols with *cis* configuration. A new reagent, **2,4-BIS-(4-METHOXYPHENYL)-1,2,3,4-DITHIADIPHOSPHETANE-2,4-DISULFIDE**, is prepared in one step from anisole and P_4S_{10} , and serves in a general method of conversion of amides to thioamides, such as **N-METHYLTHIOPYRROLIDONE**. A powerful phosphorylating and acyl coupling reagent is **DIPHENYL PHOSPHORAZIDATE**, which is prepared in a simple way. Several quite different synthesis conversions have been developed with this reagent, and a general ring contraction procedure is exemplified by turning cyclododecanone into **CYCLOUNDECANECARBOXYLIC ACID**. The final specific reagent synthesis provides an unusual heterocyclic system, **THIETE 1,1-DIOXIDE** and **3-CHLOROTHIETE 1,1-DIOXIDE**. These reactive compounds are precursors of various heterocycles and of vinylsulfene, and have served as dienophiles in the Diels–Alder reaction.

Reduction of aryl diazonium salts with $Ti(III)$ produces aryl radicals which couple efficiently with the β -position of α,β -unsaturated carbonyl compounds. The overall result is arylation of electron-deficient alkenes; **4-(*p*-CHLOROPHENYL)BUTAN-2-ONE** is obtained from 4-chlorobenzenediazonium chloride and methyl vinyl ketone. Remarkable selectivity in halogen–lithium exchange at low temperature allows formation of aryllithium reagents with chloroalkyl side chains. At higher temperatures direct ring closures occur, giving in this example **4,5-METHYLENEDIOXYBENZOCYCLOBUTENE**. The aryllithium can be intercepted by electrophiles such as a nitrile, leading to new ring systems. An example is the preparation of a **2-PHENYL-DIHYDROISOQUINOLINE**.

Titanium(IV) is a powerful but selective Lewis acid which can promote the coupling of allylsilanes with carbonyl compounds and derivatives. In the presence of titanium tetrachloride, benzalacetone reacts with allyltrimethylsilane by 1,4-addition to give **4-PHENYL-6-HEPTEN-2-ONE**. Similarly, the enol silyl ether of cyclopentanone is coupled with *t*-pentyl chloride using titanium tetrachloride to give **2-(*tert*-PENTYL)CYCLOPENTANONE**, an example of α -*tert*-alkylation of ketones.

Photochemical [2 + 2] cycloaddition is a powerful way to produce cyclobutanes, which, in turn, are reactive synthesis intermediates. *N*-Methylpyrrole adds aldehydes via [2 + 2] photocycloaddition to give transient oxetanes with high regioselectivity. Ring-opening produces 3-(α -hydroxyalkyl)pyrroles which are oxidized easily to 3-arylpyrroles, such as **3-BUTYROYL-1-METHYLPYRROLE**. With a special apparatus, ethylene is conveniently added to 3-methyl-

2-cyclohexenone to give **6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE**. Intramolecular [2 + 2] photocycloaddition of a diolefin is promoted by Cu(I). The specific example here carries an allylic hydroxyl group without interference and leads, after oxidation, to **3,3-DIMETHYL-cis-BICYCLO[3.2.0]-HEPTAN-2-ONE**.

It is well known that α,β -unsaturated ketones and aldehydes can be converted into β -bromoketals and acetals, which are generally useful synthesis intermediates. An improved procedure employs a small amount of dicinnamalacetone as indicator during addition of HBr to the unsaturated carbonyl compound. Both **2-(2-BROMOETHYL)-1,3-DIOXANE** (from acrolein) and **2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE** (from methyl vinyl ketone) are obtained in good yield on large scale. A general reduction method for converting quinones to arenes employs hydriodic acid and is particularly effective for large polynuclear aromatics, such as **BENZ[a]ANTHRACENE**.

An important biological process is the basis for a general coupling method of aldehydes into symmetrical acyloins, such as **BUTYROIN**. The key catalyst is 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, an analog of thiamin. Condensation of ketones and aldehydes with excess acetonitrile can be accomplished in a simple way to produce α,β -unsaturated nitriles. Cyclohexanone leads to **CYCLOHEXYLIDENEACETONITRILE** while benzaldehyde gives **CINNAMONITRILE**.

Cyanohydrin trimethylsilyl ethers are generally useful as precursors of "carbonyl anion equivalents" and as protected forms of aldehydes. Direct conversion of *p*-anisaldehyde into **O-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE** employs a convenient *in situ* generation of trimethylsilyl cyanide from chlorotrimethylsilane. A general synthesis of allenic esters is a variant of the Wittig reaction. Ethyl (triphenylphosphoranylidene)acetate converts propionyl chloride into **ETHYL 2,3-PENTADIENOATE**.

The Board of Editors welcomes both the submission of preparations for future volumes and suggestions for change that will enhance the usefulness of *Organic Syntheses*. Submitters are kindly asked to examine the instructions appearing before the Preface in this volume that describe the type of preparations we wish to receive and also the information to be included in each contribution. A Style Guide for preparing manuscripts is available from the Secretary to the Board, and submitters are requested to follow its instructions.

Professor Jeremiah P. Freeman, current Secretary to the Board, has carried on the voluminous correspondence with the submitters and the checkers behind the scenes and provided valuable guidance to the Editor-in-Chief. The *Chemical Abstracts* names and registry numbers in the appendix following each procedure

were found and compiled by Dr. Theodora W. Greene, who also helped edit this volume. Special acknowledgment is due to Professor Carl R. Johnson, currently Treasurer of *Organic Syntheses, Inc.* for overseeing the publication of the soft-cover version of Volume 62. Finally, I would like to thank Mrs. Myra Martin at Notre Dame and Mrs. Beth Ebling at Princeton for their help in preparing the final edition.

MARTIN F. SEMMELHACK

Princeton, New Jersey
July 1984

CONTENTS

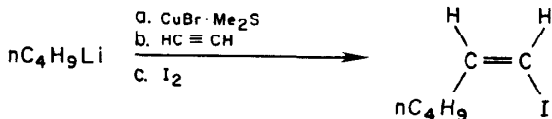
Z-1-iodohexene	1
A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF METHYL KETONES FROM TERMINAL OLEFINS: 2-DECANONE	9
β -ALKYL- α,β -UNSATURATED ESTERS FROM ENOL PHOSPHATES OF β -KETO ESTERS: METHYL 2-METHYL-1-CYCLOHEXENE-1-CARBOXYLATE ...	14
THE C-ARYLATION OF β -DICARBONYL COMPOUNDS: ETHYL 1-p- METHOXYPHENYL)-2-oxocyclohexanecarboxylate	24
PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY ALLYLATION OF ALKENYLALANES: α -FARNESENE	31
PALLADIUM-PHOSPHINE COMPLEX CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES: (Z)- β -[2-(N,N-DIMETHYLAMINO)PHENYL]-STYRENE	39
cis-N-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE	48
SILYLATION OF 2-METHYL-2-PROPEN-1-OL DIANION: 2-(HYDROXYMETHYL)- ALLYLTRIMETHYLSILANE	58
REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS; 4-(4-CHLOROPHENYL)-BUTAN-2-ONE	67
SELECTIVE HALOGEN-LITHIUM EXCHANGE REACTIONS OF 2-(2'-HALOPHENYL)-ETHYL HALIDES: SYNTHESIS OF 4,5- METHYLENEDIOXYBENZOCYCLOBUTENE AND 1-PHENYL- 3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE	74
CONJUGATE ALLYLATION OF α,β -UNSATURATED KETONES WITH ALLYLSILANE: 4-PHENYL-6-HEPTEN-2-ONE	86
α -tert-ALKYLATION OF KETONES: 2-tert-PENTYLCYCLO- PENTANONE	95
PREPARATION OF HALIDE-FREE METHYLLITHIUM	101
3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE AND 3-BUTYROYL- 1-METHYLPYRROLE	111
PHOTOCYCLIZATION OF AN ENONE TO AN ALKENE: 6-METHYLBICYCLO[4.2.0]- OCTAN-2-ONE	118
COPPER (I)-CATALYZED PHOTOCYCLOADDITION: 3,3- DIMETHYL-cis-BICYCLO[3.2.0]HEPTAN-2-ONE	125
SYNTHESIS OF AZULENE	134

β -HALOACETALS AND -KETALS: 2-(2-BROMOETHYL)-	
1,3-DIOXANE AND 2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-	
1,3-DIOXANE	140
SYNTHESIS AND DIELS-ALDER REACTION OF 3-ACETYL-2(3H)-OXAZOLONE	149
THIATION WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE 2,4-	
DISULFIDE: N-METHYLTHIOPYRROLIDONE	158
REDUCTION OF QUINONES WITH HYDRIODIC ACID: BENZ[a]ANTHRACENE	165
ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS: BUTYROIN	170
SYNTHESIS OF α,β -UNSATURATED NITRILES FROM	
ACETONITRILE: PREPARATION OF CYCLOHEXYLIDENE-	
ACETONITRILE AND CINNAMONITRILE	179
DIPHENYL PHOSPHORAZIDATE	187
CYCLOUNDECANECARBOXYLIC ACID	191
In Situ CYANOSILYLATION OF CARBONYL COMPOUNDS: O-TRIMETHYLSILYL-4-	
METHOXYMANDELONITRILE	196
α -ALLENIC ESTERS FROM α -PHOSPHORANYLIDENE ESTERS	
AND ACID CHLORIDES: ETHYL 2,3-PENTADIENOATE	202
THIETE 1,1-DIOXIDE AND 3-CHLOROTHIETE 1,1-DIOXIDE	210
LIST OF UNCHECKED PROCEDURES	218
CUMULATIVE AUTHOR INDEX FOR VOLUMES 60, 61, AND 62	223
CUMULATIVE SUBJECT INDEX FOR VOLUMES 60, 61, AND 62	226

ORGANIC SYNTHESSES

Z-1-iodohexene

(1-Hexene, 1-iodo-, (Z)-)



Submitted by A. Alexakis, G. Cahiez, and J. F. Normant¹.

Checked by J. Gabriel, P. Knochel, and Dieter Seebach.

1. Procedure

A. *Preparation of an ether solution of lithium dibutylcuprate.* A 500-mL flask (Fig. 1) with a side arm is equipped with a magnetic stirring bar, rubber septum, and three-way stopcock, on top of which is attached a rubber balloon, D. A Pt-100-thermometer, E, is inserted into the flask through the septum (Note 1). The air in the flask is replaced by dry nitrogen (Note 2). The flask is charged with 10.8 g (0.0525 mol) of cuprous bromide-dimethyl sulfide complex (Note 3) and 100 mL of ether, then immersed in a bath at -50°C; 0.10 mol of n-butyllithium, ca. 1.6 M solution in hexane, (Note 4) is added dropwise, with stirring, via a syringe inserted through the rubber septum, at such a rate that the temperature of the reaction mixture does not exceed -20°C.

After the addition is complete, stirring is continued at -30°C for 10 min to produce a grey-blue or dark blue solution of the cuprate (Note 5).

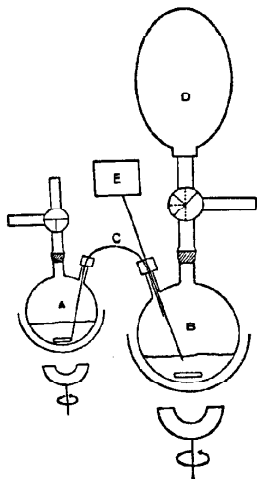


Figure 1

B. *Preparation of a solution of lithium di(*z*-hexenyl)cuprate.* A needle connected to an acetylene supply (Note 6) is introduced through the rubber septum of the flask, with its end at least 1 cm below the surface of the cuprate solution. The stopcock is fully opened towards the balloon, the solution is cooled to -50°C , and 2.64 L (0.11 mol) of acetylene (Note 6) is bubbled into the stirred cuprate solution, the temperature of which should not rise above -25°C . The gas inlet is removed and the greenish solution is stirred at -25°C for 30 min.

C. *Preparation of Z-iodohexene.* A dry, 100-mL flask with a side arm is charged with 26.7 g (0.105 mol) of iodine, equipped with a stirring bar, three-way stopcock, and rubber septum, and flushed with argon as described above (Part A). The iodine is dissolved by introducing, with stirring, 30 mL of tetrahydrofuran through the septum with a syringe. Flask A, which contains the iodine solution, is connected to flask B, which contains the vinyl cuprate solution as shown in Figure 1. The cuprate solution is kept between -60° and -50°C while the iodine solution is pushed through the Teflon tubing, C. Then the cooling bath is removed and the temperature is allowed to rise to -10°C , whereupon a precipitate of copper(I) iodide is formed, and the mixture turns yellow. After 10 min at -10°C , a mixture of 100 mL of saturated aqueous ammonium chloride and 10 mL of saturated sodium bisulfite is added with vigorous stirring. The mixture is filtered by suction through 10 g of Celite on a sintered glass funnel (#3), the contents of the funnel are washed twice with 50 mL of ether, and the filtrate is separated into two layers (Note 7). The inorganic layer is washed twice with 50 mL of pentane, and the combined organic layers are washed with aqueous sodium bisulfite (Note 8) and saturated ammonium chloride solution, and dried over anhydrous MgSO_4 . The solvents are removed by distillation through a 20-cm Vigreux column at atmospheric pressure. A spatula of copper powder is added to the residue, and the stirred mixture is distilled under reduced pressure through a 10-cm Vigreux column to give 13.5-15.5 g (65-75%) of Z-1-iodohexene, bp $47^{\circ}\text{C}/(15\text{ mm})$ (Notes 9 and 10).

2. Notes

1. The technique used here has been described previously by the checkers.² Instead, the submitters used a dry 500-mL, three-necked flask equipped with a variable speed mechanical stirrer, a 100-mL pressure-equalizing dropping funnel topped by a gas inlet and a Claisen head containing a low temperature thermometer (-70°C to +35°C), and a bubbler. A stream of nitrogen followed from the gas inlet.

2. This manipulation is described in detail in *Org. Synth.* 1971, 51, 39.

3. This complex³ should be used when the organolithium is in solution in a hydrocarbon solvent. For organolithium reagents prepared in ether (see Note 4), the same complex may be used or, more conveniently, copper iodide (CuI) can be used. The CuI purchased from Prolabo or Merck & Company, Inc. may be used directly. Other commercial sources of CuI (Fluka, Aldrich Chemical Company, Inc., Alfa Products, Morton/Thiokol, Inc.) furnish a salt which affords better results when purified. 1 mol of CuI is stirred for 12 hr with 500 mL of anhydrous tetrahydrofuran, then filtered on a sintered glass funnel (#3), washed twice with 50 mL of anhydrous tetrahydrofuran, once with 50 mL of anhydrous ether and finally dried under reduced pressure (0.1 mm) for 4 hr.

4. n-Butyllithium was used as purchased from Aldrich Chemical Company, Inc., Fluka, or Metallgesellschaft (Frankfurt). Ethereal solutions of n-butyllithium may also be used. Other organolithium compounds are easily prepared in ether; the following is representative.

Under an atmosphere of argon, a solution of n-butyl bromide (137 g, 1 mol) in anhydrous ether (500 mL) is added with stirring to small chips of lithium containing 1-2% of sodium (15.5 g, 2.2 g-atom) in ether (150 mL). The

reaction starts after the addition of about 40 mL of butyl bromide solution at room temperature. The temperature rises and the lithium metal becomes bright. If the reaction does not start, the addition of a small amount of 1,2-dibromoethane (1 mL) is often effective. Then the reaction mixture is cooled (-5°C to -10°C) and addition of the butyl bromide solution is continued slowly (about 4 hr). At the end of the addition, the solution is stirred for 2 hr at -5°C to -10°C ; then the reaction mixture is allowed to warm to room temperature. After 2 hr, excess lithium metal is removed. For many purposes, the use of a clear solution, obtained after the reaction mixture has stood overnight at 0° to -5°C , is preferable. n-Butyllithium in ether can be stored under an argon atmosphere without decomposition for 15 days at 0°C or for 2 months at -15°C .

5. During all of the operations, the rate of stirring is adjusted to avoid splashing the wall of the flask; above -10°C , thermal decomposition of the cuprate occurs. This is indicated by the presence of a black suspension, which is also formed if a copper(I) salt of insufficient purity is used, or when oxygen gets into the reaction flask.

6. The proper volume of acetylene is measured with a water gasometer as described in *Org. Synth., Collect. Vol. 1* 1941, 230, with two modifications: (a) Two traps immersed in an acetone-dry ice bath at -65°C are placed between the acetylene tank and the gasometer in order to remove acetone. (b) The washing bottles between the gasometer and the reaction flask are replaced by a drying tube (2 x 30-cm column packed with anhydrous CaCl_2).

The apparatus must be flushed with acetylene in order to remove all traces of oxygen. Acetylene dissolved in acetone is most appropriate. Acetylene obtained from tanks which contain solvents such as dimethylformamide (or other solvents) gave lower yields of carbocupration.

7. If a precipitate appears in the filtrate, filtration is repeated until two layers can be clearly distinguished.

8. A mixture of 10 mL of saturated sodium bisulfite and 50 mL of water is used. One or more washings with sodium bisulfite solution are necessary if iodine is present.

9. The sample thus obtained is >99% pure by GC analysis (3% OV 101 in a 2-m x 4-mm glass column, on Chromosorb G, with an injection temperature of 175°C, raised 100°C in 5 min, then 5°C/min).

10. The ^1H NMR spectrum of Z-1-iodohexene (in CCl_4) is as follows: δ : 6.12 (m, 2 H), 2.12 (m, 2 H, $-\text{CH}_2-\text{C}=\text{}$), 1.42 (m, 4 H, $-\text{CH}_2-$), 0.94 (m, 3 H).

3. Discussion

1-Iodoalkenes of the Z configuration are usually prepared by hydroboration of 1-iodoalkynes. The present method affords a product of higher configurational purity and constitutes an easier way to obtain such compounds in high yield, starting from less expensive reagents. In addition, the reaction can be performed easily on a larger scale (the submitters have prepared up to 1.8 mol of dialkenyl cuprate). The Z-1-iodo-1-alkenes shown in Table I have been prepared by the submitters.

TABLE I
EXAMPLES OF ALKENYL IODIDE PREPARATION FROM CARBO-CUPRATION

Entry	Organolithium	Product ^a	Yield(%)
1.	EtLi	EtCH=CHI	72
2.	$n\text{-C}_5\text{H}_{11}\text{Li}$	$(n\text{-C}_5\text{H}_{11})\text{CH=CHI}$	89
3.	$n\text{-C}_7\text{H}_{15}\text{Li}$	$(n\text{-C}_7\text{H}_{15})\text{CH=CHI}$	90
4.	$\text{EtCH=CHCH}_2\text{CH}_2\text{Li}$	$\text{EtCH=CHCH}_2\text{CH}_2\text{CH=CHI}$	79
5.	$\text{RO(CH}_2)_3\text{Li}^b$	$\text{HO(CH}_2)_3\text{CH=CHI}^c$	58
6.	$\text{RO(CH}_2)_8\text{Li}^b$	$\text{HO(CH}_2)_8\text{CH=CHI}^c$	70

^aAll alkenes, reactants and products, are Z. ^bR=CHMeOEt. ^cAfter acid hydrolysis.

This reaction illustrates a stereoselective preparation of (Z)-vinyllic cuprates,^{4,5} which are very useful synthetic intermediates. They react with a variety of electrophiles such as carbon dioxide,^{5,6} epoxides,^{5,6} aldehydes,⁶ allylic halides,⁷ alkyl halides,⁷ and acetylenic halides;⁷ they undergo conjugate addition to α,β -unsaturated esters,^{5,6} ketones,⁶ aldehydes,⁶ and sulfones.⁸ Finally they add smoothly to activated triple bonds⁶ such as $\text{HC}\equiv\text{C-OEt}$, $\text{HC}\equiv\text{C-SEt}$, $\text{HC}\equiv\text{C-CH(OEt)}_2$. In most cases these cuprates transfer both alkenyl groups. The uses and applications of the carbocupration reaction have been reviewed recently.⁹ The configurational purity in the final product is at least 99.9% Z in the above transformations.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Acetylene (8); Ethyne (9); (74-86-2)

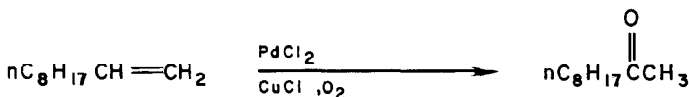
Iodine (8,9); (7553-56-2)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Z-1-Iodohexene: 1-Hexene, 1-iodo-, (Z)- (16538-47-9)

Copper iodide (8,9); (7681-65-4)

**A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF METHYL KETONES
FROM TERMINAL OLEFINS: 2-DECANONE**



Submitted by Jiro Tsuji, Hideo Nagashima, and Hisao Nemoto¹.

Checked by Edwin Vedejs, J. Gegner, and T. K. Mallman.

1. Procedure

A 100-mL, 3-necked, round-bottomed flask is fitted with a magnetic stirrer and a pressure-equalizing dropping funnel containing 1-decene (4.2 g, 30 mmol). The flask is charged with a mixture of palladium chloride (0.53 g, 3 mmol), cuprous chloride (2.97 g, 30 mmol) (Note 1) and aqueous dimethylformamide (DMF: H₂O = 7:1, 24 mL). With the other outlets securely stoppered and wired down, an oxygen-filled balloon (Note 2) is placed over one neck, and the flask is stirred at room temperature to allow oxygen uptake (Note 3). After 1 hr, 1-decene (4.2 g, 30 mmol) (Note 4) is added over 10 min (Note 5) using the dropping funnel, and the solution is stirred vigorously at room temperature under an oxygen balloon (Note 6). The color of the solution turns from green to black within 15 min and returns gradually to green. After 24 hr, the mixture is poured into cold 3N hydrochloric acid (100 mL) and extracted with five 50-mL portions of ether. The extracts are combined and washed successively with 50 mL of saturated sodium bicarbonate solution, 50 mL of brine, and then dried over anhydrous magnesium sulfate. After filtration,

the solvent is removed by evaporation and the residue is distilled using a 15-cm Vigreux column to give 2-decanone as a colorless oil (3.0-3.4 g, 65-73%, bp 43-50°C/1 mm (Notes 7, 8).

2. Notes

1. Cupric chloride can be used, but it tends to chlorinate the products and cuprous chloride is preferable; reagent grade dimethylformamide (DMF) was distilled before use.

2. The balloon was bought at a toy shop; inflated volume was approximately 500 mL.

3. The initial black solution gradually turns green by oxygen absorption.

4. The sample of 1-decene was obtained from the Aldrich Chemical Company and distilled before use.

5. In cases where the alkene is soluble, up to 30% of the aqueous DMF can be mixed with the alkene to facilitate controlled addition. With 1-decene, DMF forms a two-phase mixture.

6. The reaction is slightly exothermic.

7. The first fraction (bp 30-40°C) contains decenes which are formed by palladium-catalyzed isomerization of 1-decene (indicated by a broad signal at δ 5.2-5.5 in the ^1H NMR spectrum).

8. The spectral properties of 2-decanone are as follows: ^1H NMR (CCl_4) δ : 2.37 (2 H, t, $J = 7$), 2.02 (3 H, s), 0.7-1.8 (15 H, complex); IR (neat) 1722 cm^{-1} .

3. Discussion

Methyl ketones are important intermediates for the synthesis of methyl alkyl carbinols, annulation reagents, and cyclic compounds. A common synthetic method for the preparation of methyl ketones is the alkylation of acetone derivatives, but the method suffers limitations such as low yields and lack of regioselectivity. Preparation of methyl ketones from olefins and acetylenes using mercury compounds is a better method. For example, hydration of terminal acetylenes using HgSO_4 ² gives methyl ketones cleanly. Oxymercuration of 1-olefins and subsequent oxidation with chromic oxide is another method.³ Preparation of an epoxide from a 1-olefin and its rearrangement catalyzed by a cobalt catalyst to give methyl ketones has been reported briefly.⁴

Compared with these methods, the palladium-catalyzed oxidation of 1-olefins described here is more convenient and practical. The industrial method of ethylene oxidation to acetaldehyde using $\text{PdCl}_2\text{-CuCl}_2\text{-O}_2$ is the original reaction of this type.⁵ The oxidation of various olefins has been carried out.^{6,7,8,9}

Use of DMF as a solvent for the oxidation of 1-olefins has been reported by Clement and Selwitz.⁶ The method requires only a catalytic amount of PdCl_2 and gives satisfactory yields under mild conditions. A small amount of olefin migration product is the only noticeable contaminant in the cases reported. The procedure can be applied satisfactorily to various 1-olefins with other functional groups. This useful synthetic method for the preparation of methyl ketones has been applied extensively in the syntheses of natural products such as steroids,¹⁰ macrolides,^{11,12} dihydrojasnone,¹³ and muscone.¹⁴ A comprehensive review article on the palladium-catalyzed oxidation of olefins has been published.¹⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

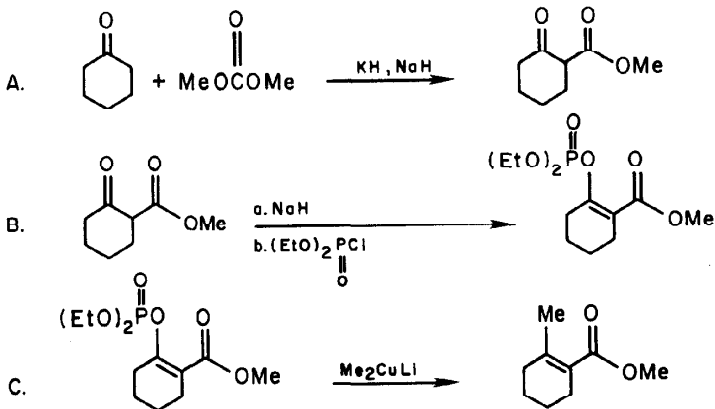
1-Decene (8,9); (872-05-9)

2-Decanone (8,9); (693-54-9)

Palladium chloride (8,9); (7647-10-1)

Cuprous chloride: Copper chloride (8,9); (7758-89-6)

**β -ALKYL- α,β -UNSATURATED ESTERS FROM ENOL PHOSPHATES OF
 β -KETO ESTERS: METHYL 2-METHYL-1-CYCLOHEXENE-1-CARBOXYLATE
 (1-Cyclohexene-1-carboxylic acid, 2-methyl, methyl ester)**



Submitted by Margot Alderdice, F. W. Sum, and Larry Weiler¹.

Checked by Stephen P. Ashburn, Clark H. Cummins, and Robert M. Coates.

1. Procedure

A. *Methyl 2-oxocyclohexanecarboxylate*. A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, reflux condenser, and a pressure-equalizing dropping funnel bearing a nitrogen inlet (Note 1). The flask is flushed with nitrogen and charged with 18.02 g (0.20 mol) of dimethyl

carbonate, 50 mL of anhydrous tetrahydrofuran, and 6.12 g (0.25 mol) of sodium hydride (Note 2). The suspension is stirred and heated to reflux temperature at which time the slow, dropwise addition of 1.80 g (0.080 mol) of cyclohexanone in 20 mL of dry tetrahydrofuran is begun. After 2 min, 0.306 g (0.0076 mol) of powdered potassium hydride (*Caution! Dry potassium hydride is pyrophoric.*) (Note 3) is added to initiate the reaction. The addition of cyclohexanone is continued over a period of 1 hr. The mixture is stirred and heated at reflux for another 30 min, cooled in an ice bath for 15-20 min, and hydrolyzed by slowly adding 75 mL of 3 M aqueous acetic acid. The contents of the flask are poured into 100 mL of aqueous sodium chloride, and the aqueous mixture is extracted with four 150-mL portions of chloroform. The organic layers are combined, dried with anhydrous sodium sulfate, and concentrated at room temperature with a rotary evaporator. Distillation of the residual liquid under reduced pressure gives 9.8-10.8 g (79-87%) of methyl 2-oxocyclohexanecarboxylate as a colorless liquid, bp 53-55°C (0.35 mm) (Note 4).

B. Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate. A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a gas inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is flushed with nitrogen and charged with 1.58 g (0.0329 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 5). The sodium hydride is freed from the mineral oil by washing with four 40-mL portions of anhydrous diethyl ether (Note 6) and withdrawing the supernatant solvent with a syringe, after which 120 mL of anhydrous ether is added. The mixture is stirred and cooled in an ice bath as 4.68 g (0.0300 mol) of methyl 2-oxocyclohexanecarboxylate (Note 7) in 10 mL of ether is added at a moderately rapid rate such that vigorous but controlled evolution of

hydrogen occurs (Note 8). The resulting creamy suspension is stirred at 0°C for another 30 min after which 4.5 mL (5.37 g, 0.031 mol) of diethyl chlorophosphate (Note 9) is injected through the septum with a syringe. The ice bath is removed, the mixture is stirred at room temperature for an additional 3 hr, and 0.6 g of solid ammonium chloride is added. Stirring is continued for 30 min, and the salts are then separated by suction filtration through a medium porosity fritted glass funnel. Concentration of the filtrate under reduced pressure affords 8.18-8.63 g of the enol phosphate which is used in Part C without purification (Note 10).

C. Methyl 2-methyl-1-cyclohexene-1-carboxylate. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a pressure-equalizing addition funnel, and an inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is charged with 8.03 g (0.042 mol) of copper(I) iodide (Note 11) and 50 mL of dry diethyl ether (Note 6), flushed with nitrogen, and cooled in an ice bath. The mixture is stirred and cooled as 92.7 mL (0.084 mol) of 1.1 M methyllithium in diethyl ether (Note 12) is added quickly through the septum by means of a syringe. The resulting clear and colorless, or light tan, solution of lithium dimethylcuprate is then cooled in a carbon tetrachloride-dry ice slush bath maintained at -23°C (Note 13). A solution of 8.18-8.63 g (ca. 0.028-0.030 mol) of the enol phosphate in 35 mL of dry ether is added from the addition funnel over 5-10 min. Stirring and cooling are continued for 3 hr after which the dark purple solution is poured into a 1-L Erlenmeyer flask containing 75 mL of ice cold 5% hydrochloric acid saturated with sodium chloride (Note 14). The mixture is stirred, or shaken vigorously, and cooled in an ice bath for 5-10 min to complete the hydrolysis. A 150-mL portion of 15% aqueous ammonia is added to the gray suspension and the mixture is swirled vigorously

for a few min until the organic layer becomes clear and the aqueous layer turns bright blue. The mixture is transferred to a separatory funnel, the aqueous layer is withdrawn, and the organic phase is washed with 50 mL of 15% aqueous ammonia. The aqueous layers are combined and extracted with one 100-mL portion of ether. The combined ethereal layers are washed with two 50-mL portions of saturated sodium chloride, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. Distillation of the remaining 4.25-5.47 g of liquid in a short-path distillation apparatus affords 3.99-4.17 g (86-90% based on β -keto ester) of methyl 2-methyl-1-cyclohexene-1-carboxylate, bp 96-97°C (27 mm) (Notes 15, 16, and 17).

2. Notes

1. The glassware was dried in an oven at 125°C and assembled while warm.

2. Dimethyl carbonate is available from Aldrich Chemical Company, Inc. The checkers dried the tetrahydrofuran immediately before use by distillation from the sodium ketyl of benzophenone under a nitrogen atmosphere. The submitters purchased sodium hydride (50% oil dispersion) from Alfa Products, Morton/Thiokol, Inc. The checkers used 12.24 g of a 50% dispersion of sodium hydride in mineral oil obtained from the same supplier. The dispersion was washed with three portions of pentane to remove the mineral oil and the remaining sodium hydride was allowed to dry under nitrogen.

3. The submitters used a 35% dispersion of potassium hydride in mineral oil supplied by Alfa Products, Morton/Thiokol, Inc.; the mineral oil was separated by washing the dispersion with five portions of dry hexane. The checkers used a 25% dispersion of potassium hydride in mineral oil obtained from the same source but without removing the mineral oil. The oil remained in the distillation pot when the product was distilled.

4. A boiling point of 68°C (0.8 mm) and a melting point of 25°C have been reported for methyl 2-oxocyclohexanecarboxylate.² The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 1745, 1715, 1615; ^1H NMR (CDCl_3) δ : 1.62 (m, 4 H, two CH_2), 2.22 (m, 4 H, two CH_2), 3.37 (t, 0.25 H, $J = 7$ Hz, CH at C-2 in keto form), 3.74 (s, 3 H, CH_3), 12.10 (s, 0.75 H, enol OH).

5. The sodium hydride-mineral oil dispersion was purchased from Alfa Products, Morton/Thiokol, Inc.

6. Diethyl ether was dried by the submitters by refluxing over lithium aluminum hydride and was distilled immediately before use. The checkers distilled diethyl ether from the sodium ketyl of benzophenone before use.

7. A mixture of methyl and ethyl 2-oxocyclohexanecarboxylate, available from Aldrich Chemical Company, Inc., may also be used. The product obtained is a mixture of methyl and ethyl 2-methylcyclohexene-1-carboxylates.

8. No gas evolution was observed by the checkers in some runs in which an older lot of sodium hydride was used. In this case, the cooling bath was removed and the mixture was allowed to stir at room temperature until the bubbling ceased.

9. Diethyl chlorophosphate, supplied by Aldrich Chemical Company, Inc., was used by the submitters without purification and was handled in a glove bag under an atmosphere of dry nitrogen in a well-ventilated hood. The reagent was distilled and stored under nitrogen by the checkers. Aliquots were withdrawn with a syringe as needed.

10. The spectral properties of the enol phosphate are as follows: IR (CHCl_3) cm^{-1} : 1715, 1660, 1290, 1030; 90 MHz ^1H NMR (CDCl_3) δ : 1.3-1.9 (m, 4 H, CH_2CH_2), 1.35 (t, 6 H, $J = 7$ Hz, OCH_2CH_3), 2.3 (m, 4 H, allylic CH_2), 3.68 (s, 3 H, OCH_3), 4.15 (quintet, 4 H, $J = 7$ Hz, OCH_2CH_3).

11. Copper(I) iodide, supplied by either MC and B Manufacturing Chemists or Fisher Scientific Company, was purified by recrystallization from water saturated with potassium iodide.^{3,4} The wet powder was washed successively with ethanol, acetone, and ether, and dried by heating overnight at 100°C in an evacuated drying pistol containing phosphorus pentoxide.^{4a,5} The submitters advise that the compound should not be dried by heating in air.⁵ When oven-dried copper(I) iodide was used in this procedure, the yield of product was somewhat lower (77-88%) and as much as 10-20% of 1-acetyl-2-methylcyclohexene was formed. It is probable that the presence of small amounts of copper(II) impurities is responsible for the increased proportion of this by-product.^{4b,6} Purified copper(I) iodide may be stored under nitrogen without change for several months.^{4a}

12. Ethereal methyllithium (as the lithium bromide complex) was obtained by the submitters from Aldrich Chemical Company Inc. The checkers used 1.19 M methyllithium-lithium bromide complex in ether supplied by Alfa Products, Morton/Thiokol, Inc. The concentration of the methyllithium was determined by titration with 1.0 M tert-butyl alcohol in benzene using 1,10-phenanthroline as indicator.⁷ The submitters report that ethereal methyllithium of low halide content purchased from Alfa Products, Morton/Thiokol, Inc., gave similar results.

13. The coupling reaction between lithium dimethylcuprate and acyclic enol phosphates must be carried out between -47 and -98°C for stereoselective formation of β -methyl- α,β -unsaturated esters.

14. The submitters have found that the reaction may also be hydrolyzed with a solution of 60 mL of saturated ammonium chloride and 15 mL of concentrated aqueous ammonia. The ethereal layer is then washed with 15% aqueous ammonia until the aqueous layer is no longer blue.

When lithium di-n-butylcuprate is used, the yields are often improved by adding 1-bromobutane to the reaction mixture before hydrolysis with aqueous ammonium chloride.

15. The product exhibits the following spectral properties: IR (CHCl_3) 1720, 1640, 1080 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.3-1.7 (m, 4 H, CH_2CH_2), 1.8-2.4 (m, 4 H, allylic CH_2), 1.97 (s, 3 H, CH_3), 3.69 (s, 3 H, OCH_3); MS (70 eV) m/e (assignment, rel intensity): 154 (M^+ , 50%), 95 ($-\text{CO}_2\text{CH}_3$, 100%).

16. The purity of the product was determined by the checkers by GLC analysis using the following column and conditions: 3-mm by 1.8-m column, 5% free fatty acid phase (FFAP) on acid-washed Chromosorb W (60-80 mesh) treated with dimethyldichlorosilane, 90°C (1 min) then 90° to 200°C (15°C per min). The chromatogram showed a major peak for methyl 2-methyl-1-cyclohexene-1-carboxylate preceded by two minor peaks for methyl 1-cyclohexene-1-carboxylate and 1-acetyl-2-methylcyclohexene. The areas of the two impurity peaks were 5-6% and 0.5-2% that of the major peak. The purity of the product seems to depend upon careful temperature control during the reaction. The total amount of the two impurities was 14-21% in runs conducted at about -15 to -20°C or at temperatures below -23°C .

17. The submitters purified the product by distillation in a Kugelrohr apparatus with an oven temperature of 85 - 88°C (20 mm) and obtained 3.80-3.85 g (88-89%). The purity of the product was 93-96% according to GLC analysis. The major impurity (2-6%) was 1-acetyl-2-methylcyclohexene.

The product may also be purified by flash chromatography⁸ using 19/1 (v/v) petroleum ether, (bp 30 - 60°C)/ethyl acetate as eluant. A column of 2-cm diameter was packed to a height of 25 cm with Kieselgel 60 (230-400 mesh) supplied by BDH Chemicals Ltd. In one run chromatography of 4.19 g of crude product afforded 3.70 g (88%) of the α,β -unsaturated ester which was

completely free of the more polar by-product, 1-acetyl-2-methylcyclohexene. However, the checkers found that the other by-product, methyl 1-cyclohexene-1-carboxylate, is not readily separated by flash chromatography.

3. Discussion

This procedure illustrates a new method for the preparation of β -alkyl- α,β -unsaturated esters by coupling lithium dialkylcuprates with enol phosphates of β -keto esters.⁹ The procedure for the preparation of methyl 2-oxocyclohexanecarboxylate described in Part A is based on one reported by Ruest, Blouin, and Deslongchamps.² Methyl 2-methyl-1-cyclohexene-1-carboxylate has been prepared by esterification of the corresponding acid with diazomethane¹⁰ and by reaction of methyl 2-chloro-1-cyclohexene-1-carboxylate with lithium dimethylcuprate.¹¹

The formation of β -alkyl- α,β -unsaturated esters by reaction of lithium dialkylcuprates or Grignard reagents in the presence of copper(I) iodide, with β -phenylthio-,^{12,13} β -acetoxy-,^{14,15} β -chloro-,^{11,16} and β -phosphoryloxy- α,β -unsaturated esters⁹ has been reported. The principal advantage of the enol phosphate method is the ease and efficiency with which these compounds may be prepared from β -keto esters. A wide variety of cyclic and acyclic β -alkyl- α,β -unsaturated esters has been synthesized from the corresponding β -keto esters.⁹ However, the method is limited to primary dialkylcuprates. Acyclic β -keto esters afford (Z)-enol phosphates which undergo stereoselective substitution with lithium dialkylcuprates with predominant retention of stereochemistry (usually > 85-98%). It is essential that the cuprate coupling reaction of the acyclic enol phosphates be carried out at lower temperatures (-47 to -98°C) to achieve high stereoselectivity. When combined with the γ -

alkylation of methyl acetoacetate dianion,¹⁷ this method provides a facile means of isoprenoid chain extension.¹⁸ The procedures have been employed to advantage in syntheses of (E,E)-10-hydroxy-3,7-dimethyldeca-2,6-dienoic acid,^{18a} latia luciferin^{18b} and mokupalide.^{18c} β -Diketones may be converted to β -alkyl- α,β -unsaturated ketones in a similar manner.⁹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 2-methyl-1-cyclohexene-1-carboxylate: 1-Cyclohexene-1-carboxylic acid, 2-methyl-, methyl ester (9); (25662-38-3)

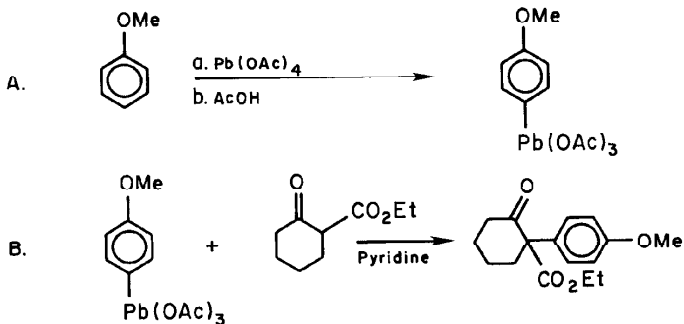
Dimethyl carbonate: Carbonic acid, dimethyl ester (8,9); (616-38-6)

Methyl 2-oxocyclohexanecarboxylate: Cyclohexanecarboxylic acid, 2-oxo-, methyl ester (9); (41302-34-5)

Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester (8,9); (814-49-3)

Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate: 1-Cyclohexene-1-carboxylic acid, 2-[(diethoxyphosphinyl)oxy]-, methyl ester (10); (71712-64-6)

THE C-ARYLATION OF β -DICARBONYL COMPOUNDS: ETHYL
1-(p-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE



Submitted by Robert P. Kozyrod and John T. Pinhey¹.

Checked by M. F. Semmelhack and David Ziering.

1. Procedure

A. *p*-Methoxyphenyllead triacetate. A 1-L Erlenmeyer flask, equipped with a magnetic stirring bar, is charged with 50 g (0.11 mol) of lead tetraacetate (Note 1), chloroform (200 mL), and 140 g (1.09 mol) of dichloroacetic acid (Note 2). To this solution is added 16 g (0.15 mol) of anisole (Note 3), and the mixture is stirred at 25°C until lead tetraacetate can no longer be detected (Note 4). The reaction mixture is washed with water (2 x 250 mL) and the chloroform solution is treated with 1.5 L of hexane (Note 5). The yellow

precipitate (44 g) is collected by suction filtration and stirred with a mixture of glacial acetic acid (250 mL) and chloroform (200 mL) for 1 hr.

The chloroform solution is washed with water (2 x 250 mL) and stirred with glacial acetic acid (250 mL) for 1 hr (Note 6). The solution that results is washed with water (2 x 250 mL), and the chloroform phase is treated with 1.5 L of hexane and kept at 2°C for 48 hr. The material which precipitates is collected and dried at 0.1 mm in a desiccator (calcium chloride) for 5 hr to give p-methoxyphenyllead triacetate (20-22 g, 35-40%) as pale yellow crystals, mp 138-139°C (Note 7). The product may be kept for at least 3 weeks if stored at 2°C in a sealed container.

B. *Ethyl 1-(p-methoxyphenyl)-2-oxocyclohexanecarboxylate*. A 250 mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 22.2 g (45 mmol) of p-methoxyphenyllead triacetate, 10.8 g (135 mmol) of pyridine (Note 8), and 70 mL of chloroform (Note 9). To this solution is added 7.0 g (41 mmol) of ethyl 2-oxocyclohexanecarboxylate (Note 10), a calcium chloride drying tube is put in place, and the mixture is stirred at 40°C (Note 11).

After 24 hr, the reaction mixture is diluted with chloroform (80 mL), and washed with water (150 mL) and 3 M sulfuric acid (2 x 150 mL). The water and sulfuric acid washings are each washed (Note 12) with 100 mL of chloroform. The combined chloroform extracts are washed with water (2 x 250 mL), dried with magnesium sulfate, and the solvent removed to give an orange-colored oil (10.3 g) which slowly crystallizes on standing. Crystallization from hexane (Note 5) gives 9.4 g (82%) of ethyl 1-(p-methoxyphenyl)-2-oxocyclohexanecarboxylate, mp 49-50°C.

2. Notes

1. Lead tetraacetate from Merck & Company, Inc. was used. Acetic acid was removed from the reagent at 0.1 mm for 24 hr, in the dark, in a desiccator containing potassium hydroxide pellets.

2. Dichloroacetic acid from Merck & Company, Inc. was used without further purification.

3. Anisole from Fluka AG was distilled before use.

4. A few drops of reaction mixture were shaken with water. A brown precipitate of PbO_2 indicates the presence of unreacted lead tetraacetate. For the quantities given, a reaction time of 1 hr at 15-20°C is adequate.

5. Hexanes, bp 60-69°C, certified by Fisher Scientific Company were used.

6. A second metathesis with glacial acetic acid is carried out to ensure complete conversion of the oligomer into the product.

7. It has been found that the yield of product is generally higher when the reaction is performed on a smaller scale. Reactions carried out on approximately one third of the above scale have given yields of approximately 60%.

8. Pyridine from Merck & Company, Inc. was distilled and stored over potassium hydroxide pellets.

9. Chloroform was dried over calcium chloride and distilled prior to use.

10. The ethyl 2-oxocyclohexanecarboxylate used was Fluka AG practical grade, and was distilled (bp 105-108°C/12 mm) before use.

11. The submitters report that after approximately 1 hr some lead(II) acetate is deposited as an orange-red gum which may temporarily restrict the motion of the stirring bar; this was not observed by the checkers. The material generally crystallizes after a short period as a white solid.

12. These washings are extracted separately in order to minimize formation of solid lead(II) sulfate.

3. Discussion

The procedure described here serves to illustrate a new, general method for effecting the α -arylation of β -dicarbonyl compounds by means of an aryllead triacetate under very mild conditions. Although the first synthesis of an aryllead triacetate was reported relatively recently, a wide range of these compounds can now be readily prepared.² The most direct route to these compounds is plumbation of an aromatic compound with lead tetraacetate, and in the procedure reported here p-methoxyphenyllead triacetate has been prepared in this way. It may also be obtained by reaction of the diarylmercury with lead tetraacetate,³ a longer, but more general method of synthesis of aryllead triacetates.

The first synthesis of p-methoxyphenyllead triacetate by direct plumbation was reported by Harvey and Norman,⁴ who obtained the compound in 24% yield by heating anisole and lead tetraacetate in acetic acid at 80°C for 4 days. Recently it has been found² that a much faster reaction and higher yield of aryllead compounds can be achieved by use of a haloacetic acid in place of acetic acid, and this has allowed the synthesis of a greater range of aryllead triacetates by direct plumbation. The improved reaction rate is presumably due to an increase in electrophilicity of lead when acetate is

exchanged for a more electron-withdrawing ligand. The choice of the haloacetic acid depends on the reactivity of the aromatic substrate; thus while dichloroacetic acid has been found best for the plumbation of anisole, trichloroacetic acid is preferred in the case of toluene and biphenyl.²

Aryllead tricarboxylates have been shown to be intermediates in two new routes to phenols,^{5,6} and to have considerable potential as reagents for the C-arylation of carbon acids which are more acidic than diethyl malonate. A study of their reactions with β -diketones,⁷ β -keto esters,⁸ and Meldrum's acid and its derivatives⁹ has established that such compounds, which contain only one replaceable hydrogen, undergo smooth arylation in high yield under the conditions outlined in this procedure. Compounds which contain two replaceable hydrogens are less predictable in their behavior. When a 1:1 ratio of substrate to aryllead compound is used, dimedone gave only diarylated product in high yield, while ethyl acetoacetate gave both mono- and di-arylated products in only moderate yield.

Recently it has been shown that triphenylbismuth carbonate¹⁰ and pentaphenylbismuth¹¹ can be used to achieve a similar arylation of β -dicarbonyl compounds. These reagents also react under very mild conditions and yields are generally high. Prior to the introduction of the organolead and organobismuth reagents, the most promising procedure for arylation of β -dicarbonyl compounds involved reaction of the enolate anion with a diaryliodonium salt, usually at 80-100°C.¹² Although only a limited range of substrates has been examined, it would appear that yields are only moderate, and in the case of dimedone a mixture of mono-, di-, and O-arylated products is produced. A further method, which has obvious limitations, involves the copper-catalyzed substitution of bromine in 2-bromobenzoic acids by the enolate anion of a β -dicarbonyl compound.¹³

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

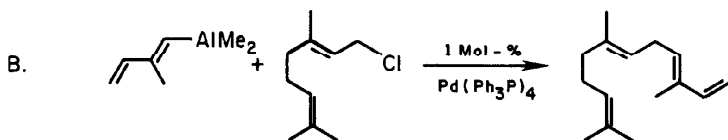
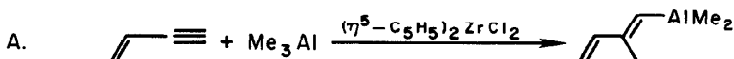
p-Methoxyphenyllead: Plumbane, triacetoxy(p-methoxyphenyl)- (8); Plumbane, tris(acetyloxy)(4-methoxyphenyl)- (9); (18619-43-9)

Lead tetracetate: Acetic acid, lead (4+) salt (8,9); (546-67-8)

Anisole (8); Benzene, methoxy- (9); (100-66-3)

Ethyl 2-oxocyclohexanecarboxylate: Cyclohexanecarboxylic acid, 2-oxo-, ethyl ester (8,9); (1655-07-8)

PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY
 ALLYLATION OF ALKENYLALANES: α -FARNESENE
 (1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-)



Submitted by Ei-ichi Negishi¹ and Hajime Matsushita².

Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

Caution! Trimethylalane (Note 1) is highly pyrophoric. It must be kept and used under a nitrogen atmosphere.

A. *(E)*-(2-Methyl-1,3-butadienyl)dimethylalane. An oven-dried, 1-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an outlet connected to a mercury bubbler is charged with 7.01 g (24 mmol) of dichlorobis(η^5 -cyclopentadienyl)zirconium (Note 2) and flushed with nitrogen. To this are added sequentially at 0°C 100 mL of 1,2-dichloroethane (Note 3), 12.48 g (120 mmol) of a 50% solution of 1-buten-3-yne in

xylene (Note 4), and 120 mL (240 mmol) of a 2 M solution of trimethylalane in toluene (Note 1). The reaction mixture is stirred for 12 hr at room temperature and used in the next step without further treatment (Note 5).

B. (3E, 6E)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (α -farnesene). To the solution of (E)-(2-methyl-1,3-butadienyl)dimethylalane prepared above are added 17.25 g (100 mmol) of geranyl chloride (Note 6) and 1.15 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 7) dissolved in 100 mL of dry tetrahydrofuran (Note 8), while the reaction temperature is controlled below 25-30°C with a water bath. After the reaction mixture is stirred for 6 hr at room temperature, 250 mL of 3 N hydrochloric acid is slowly added at 0°C. The organic layer is separated and the aqueous layer is extracted twice with pentane. The combined organic layer is washed with water, saturated aqueous sodium bicarbonate, and water. After the organic extract is dried over anhydrous magnesium sulfate, the solvent is removed thoroughly using a rotary evaporator (15-20 mm), and the crude product is passed through a short (15-20 cm) silica gel column (60-200 mesh) using hexane as an eluent (Note 9). After the hexane is evaporated using a rotary evaporator, the residue is distilled using a 12-cm Vigreux column to give 16.70 g (83% based on geranyl chloride) of α -farnesene as a colorless liquid, bp 63-65° (0.05 mm) (Note 10).

2. Notes

1. The submitters used trimethylalane available in a cylinder from Ethyl Corporation. Both neat trimethylalane and its 2 M solution in toluene gave comparable results. The toluene solution of trimethylalane is also available from Aldrich Chemical Company.

2. The submitters used dichlorobis(η^5 -cyclopentadienyl)zirconium available from Aldrich Chemical Company. This chemical is sufficiently air-stable to be handled in air.

3. The 1,2-dichloroethane available from Aldrich Chemical Company was distilled from phosphorus pentoxide before use. Although less effective, dichloromethane may also be used in the carbometallation step.

4. The submitters used a 50% solution of 1-buten-3-yne in xylene, available from Chemical Samples Company. For transferring this solution, the following procedure may be recommended. An ampule containing the solution is cooled with an ice-salt bath, opened, and capped with a rubber septum. A weighed measuring flask capped with a rubber septum is cooled with the ice-salt bath. To this is introduced the cooled solution by means of a double-tipped needle, and the weighed solution is then introduced to the reaction flask by means of a double-tipped needle.

5. The reaction mixture containing (E)-(2-methyl-1,3-butadienyl)dimethylalane may be stored at room temperature for at least a few days. Although it appears to be stable at room temperature for a much longer period of time, its thermal stability has not been carefully determined. The cross-coupling reaction in Section B should require only one equivalent of the alkenylalane, and its yield by gas chromatographic examination is 90-100%. It is practical, however, to use ca. 20% excess of 1-buten-3-yne for preparing the alkenylalane so as to achieve a high-yield conversion of geranyl chloride into α -farnesene.

6. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, with carbon tetrachloride and triphenylphosphine according to an Organic Syntheses procedure (Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, 54, 63).

7. Tetrakis(triphenylphosphine)palladium was prepared by treating palladium chloride, available from Matthey Bishop, Inc., with hydrazine hydrate in the presence of triphenylphosphine according to an Inorganic Syntheses procedure.³ The submitters used a freshly prepared, shiny yellow, crystalline sample of the palladium complex. On standing for an extended period of time (> a few weeks), its color gradually darkens. Even such samples are effective in many palladium-catalyzed cross-coupling reactions,⁴ but have not been tested in this reaction. Tetrakis(triphenylphosphine)palladium is also available from Aldrich Chemical Company.

8. Tetrahydrofuran available from Aldrich Chemical Company was distilled from sodium and benzophenone.

9. The main purpose of this filtration is to remove traces, if any, of palladium-containing compounds that might induce undesirable transformations, such as isomerization and polymerization, during the subsequent distillative workup.

10. The submitters reported bp 73-75°C (0.05 mm). Gas chromatographic examination of the reaction mixture with a hydrocarbon internal standard indicates that α -farnesene is formed in 98% yield, based on geranyl chloride, essentially as a single product (>98%). The product obtained by this procedure shows the following properties: n_D^{23} 1.4977; IR (neat) cm^{-1} : 3080(w), 2960(s), 2900(s), 1664(w), 1635(m), 1601(m), 981(m), 883(s); ^1H NMR [CDCl_3 , $(\text{CH}_3)_4\text{Si}$] δ : 1.59 (s, 3 H), 1.63 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 2.03 (m, 4 H), 2.82 (t, $J = 6, 2$ H); ^{13}C NMR [CDCl_3 , $(\text{CH}_3)_4\text{Si}$] δ : 11.62, 16.07, 17.63, 25.69, 26.89, 27.35, 39.88, 110.37, 122.36, 124.50, 131.10, 131.74, 133.79, 135.55, 141.69.

3. Discussion

This procedure for the synthesis of α -farnesene⁵ is representative of the palladium-catalyzed stereo- and regiospecific coupling of allylic derivatives with alkenyl- and arylmetals.⁶ The use of neryl chloride in place of geranyl chloride gives the 6-Z isomer of α -farnesene in 77% yield (>98% isomeric purity).⁶ The high stereo- and regiospecificity (>98%) has been observed only with γ,γ -disubstituted allylic electrophiles. With γ -monosubstituted allylic derivatives, varying amounts of stereo- and regio-isomers have been observed.⁷

Various allyl derivatives, such as those containing acyloxy, dialkylaluminoxy, and trialkylsilyloxy groups, also react with alkenylalanes in the presence of a palladium-phosphine catalyst,⁷ and the synthesis of α -farnesene has been achieved by using geranyl acetate. Although the observed yields are ca. 20% lower than those observed with geranyl chloride, a careful comparison of the two derivatives has not been performed. In general, the order of reactivity of various leaving groups is: $-\text{Cl} > -\text{OAc} > -\text{OP}(\text{OR})_2 > -\text{OSiR}_3$.

In addition to alkenylalanes, readily obtainable by either hydroalumination⁸ or carboalumination⁹ of alkynes, alkenylzirconium derivatives,^{6,10} obtainable by hydrozirconation¹¹ of alkynes, undergo a related alkenyl-allyl coupling reaction. In a related aryl-allyl coupling reaction catalyzed by palladium complexes, arylmetals containing magnesium, zinc, and cadmium, in addition to those containing aluminum and zirconium, give the expected cross-coupled products. The yields with zinc or cadmium tend to be higher than those with aluminum or zirconium, whereas magnesium, in this respect, is inferior to aluminum or zirconium.⁷ Related reactions of alkenylboranes¹² and alkenylmercury compounds¹³ are also known, but their applicability to the selective synthesis of 1,4-dienes of terpenoid origin, such as α -farnesene, is unknown.

The synthesis of 1,4-dienes via cross coupling can, in principle, be achieved either by the reaction of allylmetals with alkenyl electrophiles or by the reaction of alkenylmetals with allyl electrophiles. The reaction of π -allylnickel derivatives with alkenyl halides¹⁴ represents the former approach and can be highly regioselective. Stereo- and regio-defined alkenylmetals containing aluminum,¹⁵ boron,¹⁶ silicon,¹⁷ and copper¹⁸ have been reported to react with allylic electrophiles producing 1,4-dienes. With the possible exception of the organocopper reaction, the scope of these uncatalyzed reactions is practically limited to γ -unsubstituted allylic halides. Finally, the nickel-catalyzed reaction of Grignard reagents with allylic electrophiles¹⁹ is also known, but the reaction is generally nonselective. Nor does it appear that the reaction has been applied to the synthesis of 1,4-dienes.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

α -Farnesene: 1,3,6,10-Dodecatetraene, 3,7,11-trimethyl- (8,9); (502-61-4)

Trimethylalane: Aluminum, trimethyl- (8,9); (75-24-1)

Dichlorobis(η^5 -cyclopentadienyl)zirconium: Zirconium, dichloro- π -cyclopentadienyl- (8); Zirconium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1291-32-3)

1-Buten-3-yne (8,9); (689-97-4)

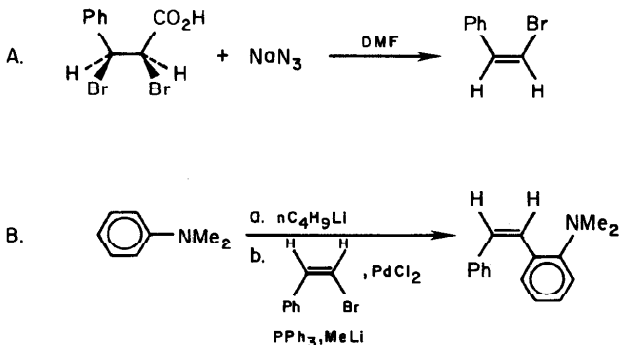
Geranyl chloride: (E)-2,6-Octadiene, 1-chloro-3,7-dimethyl- (8,9), (5389-87-7)

Tetrakis(triphenylphosphine)palladium: Palladium, tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

PALLADIUM-PHOSPHINE COMPLEX CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND

ALKENYL HALIDES: (Z)- β -[2-(N,N-DIMETHYLAMINO)PHENYL]STYRENE

(Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)-)



Submitted by Shun-Ichi Murahashi, Takeshi Naota, and Yoshio Tanigawa¹.

Checked by Joseph Fortunak and Ian Fleming.

1. Procedure

Caution! The reaction in Part A should be carried out in a well-ventilated hood because bromine is toxic.

A. (Z)- β -Bromostyrene. In a 1-L, round-bottomed flask equipped with a magnetic stirring bar are placed 30.8 g (0.100 mol) of *erythro*- α,β -dibromo- β -phenylpropionic acid (Note 1), 13.0 g (0.200 mol) of sodium azide (Note 2),

and 500 mL of dry *N,N*-dimethylformamide (Note 3). The reaction mixture is stirred at room temperature for 8 hr, and poured into a mixture of 300 mL of ether and 300 mL of water. The organic layer is separated, washed with three 100 mL portions of water, dried over magnesium sulfate, and filtered. After evaporation of the filtrate with a rotary evaporator, the residual liquid is distilled under reduced pressure giving 13.5-13.9 g (74-76%) of (Z)- β -bromostyrene, bp 54-56°C (1.5 mm). (Note 4).

B. *2-(N,N-Dimethylamino)phenyllithium*. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser connected to a nitrogen-inlet tube is capped with serum stoppers and flushed with nitrogen. The flask is charged with 18.2 g (0.150 mol) of *N,N*-dimethylaniline (Note 5) and 33.4 mL (0.050 mol) of a 1.50 M solution of *n*-butyllithium in hexane (Note 6). While a continuous positive nitrogen pressure is maintained, the solution is heated at reflux (in a 90-95°C bath) with stirring for 20 hr and then cooled to room temperature (Note 7).

C. (Z)- β -[2-(*N,N*-Dimethylamino)phenyl]styrene. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser connected to a nitrogen-inlet tube, and a 300-mL, pressure-equalizing dropping funnel is capped with serum stoppers. The flask is flushed with nitrogen and charged with 0.433 g (0.0025 mol) of palladium chloride (Note 8), 2.62 g (0.010 mol) of triphenylphosphine (Note 9), and 300 mL of benzene (Note 10). While a continuous positive nitrogen pressure is maintained, the mixture is stirred at gentle reflux for 30 min, and then 4.25 mL (0.0060 mol) of a 1.41 M solution of methyllithium in ether (Note 11) is added with a syringe. After an additional 10 min at reflux, 9.15 g (0.050 mol) of (Z)- β -bromostyrene prepared in Part A is added in one portion with a syringe, and the mixture is

heated at reflux for 10 min. The solution of 2-(N,N-dimethylamino)phenyllithium prepared in Part B is transferred to the dropping funnel with a syringe, and diluted by adding 150 mL of benzene (Notes 10 and 12). The resulting solution is then added dropwise to the mixture with stirring at reflux over a period of 30 min (Note 13). After additional stirring for 10 min, the resulting red solution is cooled to room temperature with the help of an ice-bath, and quenched by adding 100 mL of saturated aqueous ammonium chloride. The organic layer is separated, washed successively with 100 mL of water and 100 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate and filtered. The solvent is evaporated with a rotary evaporator and the residue is distilled under reduced pressure to give a forerun (ca. 11 g) of excess N,N-dimethylaniline, bp 31-51°C (1 mm), followed by 7.4-7.5 g (66-67%) of (Z)- β -[2-(N,N-dimethylamino)phenyl]styrene, bp 90.0-92.0°C (0.035 mm), 82-84°C (0.01 mm), as a pale yellow liquid (Note 14).

2. Notes

1. *erythro*- α,β -Dibromo- β -phenylpropionic acid is prepared from trans-cinnamic acid (mp 133-134°C) (Nakarai Chemicals, Japan) by the method used for ethyl α,β -dibromo- β -phenylpropionate (Abbott T. W.; Althousen, D. *Org. Synth., Coll. Vol. 2* **1943**, 270) in 83% yield, mp 199-200°C. The checkers used benzene (400 mL per mol) in place of the carbon tetrachloride, because the mixture was then easier to stir and the reaction was more reproducible. The yield before purification was 89% (mp 174-191°C); the yield after recrystallization was 81% (mp 198-199°C). Crude material could be used without appreciable loss of yield.

2. Sodium azide from Wako Pure Chemical Ind., Japan, was used without purification.

3. N,N-Dimethylformamide is distilled over calcium hydride.

4. Gas chromatographic analysis of the distillate (10% PEG-20M on 60-80 mesh, Celite 545 AW, 1-m x 4-mm, column temperature 100-220°C, injection temperature 200°C) shows that the product is 100% isomerically pure. The spectral properties of the (Z)- β -bromostyrene are as follows: IR (neat) cm^{-1} : strong absorptions at 3095, 3040, 1620, 1500, 1450, 1333, 1032, 930, 920, 830, 770, and 700; ^1H NMR (CHCl_3) δ : 6.43 (doublet, 1 H, $J=8$, $\text{PhCH}=\text{C}$), 7.08 (doublet, 1 H, $J=8$, $\text{PhC}=\text{CHBr}$), 7.22-7.85 (multiplet, 5 H, aromatic). The checkers also purified the residual oil before distillation by filtration in 250 mL of pentane through three times its weight of silica gel (70-230 mesh) followed by evaporation. The yield before distillation was then reproducibly 84%, distillation was avoided, and the next step proceeded with undiminished yield.

5. N,N-Dimethylaniline from Nakarai Chemicals was dried over calcium hydride and freshly distilled. Three molar equivalents of N,N dimethylaniline are used to achieve complete conversion of the n-butyllithium, because in the present particular case free n-butyllithium, if present, causes the isomerization of the (Z)-alkene to the (E)-isomer.

6. A solution of n-butyllithium in hexane was obtained from Aldrich Chemical Company, Inc. Before use the solution is titrated with a 1 M solution of 2-butanol in xylene according to the procedure of Watson and Eastham,² [see Gall, M.; House, H. O. *Org. Synth.* **1972**, *52*, 39] with 2,2'-biquinoline as indicator.

7. The resulting cloudy, yellowish orange solution should be used within 3-4 hr.

8. Palladium chloride from Inuishi Precious Metal Company, Japan, was used without purification.

9. Triphenylphosphine from Nakarai Chemicals, Japan, was used without purification.

10. Benzene is distilled over benzophenone ketyl and stored under a nitrogen atmosphere.

11. A solution of methyllithium in ether is prepared from lithium wire and methyl bromide according to the literature procedure,³ and titrated by the same method as Note 6. The checkers used 1.1 M methyllithium from Aldrich.


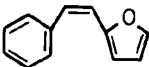

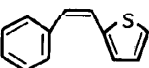
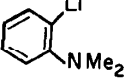
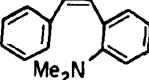

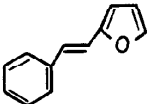
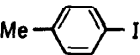
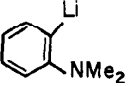
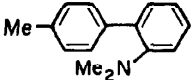
12. Without the dilution, (Z)-1,4-diphenyl-1-buten-3-yne is detected, apparently formed from the cross-coupling with phenylacetylide, derived from lithiation of β -bromostyrene, followed by E2cB elimination or Fritsch-Butlenberg-Wiechell type rearrangement.

13. Prolonged reaction time causes the isomerization of (Z)- β -[2-(N,N-dimethylamino)phenyl]styrene to the (E)-isomer.

14. Gas chromatographic analysis of the product (5% silicone SE 30 on 80-100 mesh Chromosorb W AB, 0.5-m x 4-mm, column temperature 100-250°C, injection temperature 180°C) shows that the product is at least 98% (Z)-isomer. The spectral properties of the (Z)-alkene are as follows; IR (neat) cm^{-1} : strong absorptions at 3070, 3025, 2950, 2870, 2035, 2780, 1600, 1490, 1450, 1320, 1190, 1160, 1140, 1100, 1050, 950, 780, 750, and 690; ^1H NMR (CCl_4) δ : 2.76 (singlet, 6 H, $\text{CH}_3\text{-N}$), 6.38 (doublet, 1 H, $J=12.3$, PhC=CH), 6.63 (doublet, 1 H, $J=12.3$, PhCH=C), 6.50-7.30 (multiplet, 9 H, aromatic).

Table I

PALLADIUM-CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES^a

Halides	RLi	Products	Yield ^b (%)
(Z)-C ₆ H ₅ CH=CHBr	CH ₃ Li	(Z)-C ₆ H ₅ CH=CHCH ₃	90
	CH ₃ (CH ₂) ₃ Li	(Z)-C ₆ H ₅ CH=CHC ₄ H ₉	62
			85
			94 ^c
			87 (66-67) ^d
	C ₆ H ₅ SLi	(Z)-C ₆ H ₅ CH=CHSC ₆ H ₅	95 ^c
(E)-C ₆ H ₅ CH=CHBr	C ₂ H ₅ SLi	(Z)-C ₆ H ₅ CH=CHSC ₂ H ₅	93 ^c
	CH ₃ Li	(E)-C ₆ H ₅ CH=CHCH ₃	88
			85
			(89) ^d

^aThe reaction was carried out on a 1.0-5.0 mmol scale. ^bDetermined by gas chromatography. ^cTetrakis(triphenylphosphine)palladium was used. ^dIsolated yield.

3. Discussion

The starting materials, (Z)- β -bromostyrene⁴ and 2-(N,N-dimethylamino)-phenyllithium⁵ have been prepared in satisfactory yields by known procedures after slight modifications. The azide procedure⁴ gives higher stereospecificity than the earlier procedure using sodium bicarbonate.⁶

This procedure illustrates a general method for the preparation of alkenes from the palladium(0)-catalyzed reaction of vinyl halides with organolithium compounds,⁷ which can be prepared by various methods, including direct regioselective lithiation of hydrocarbons.⁸ The method is simple and has been used to prepare a variety of alkenes stereoselectively. Similar stoichiometric organocopper reactions sometimes proceed in a nonstereoselective manner⁹ and in low yields.¹⁰ Nickel catalysts can be used efficiently for the reaction of alkenyl halides with Grignard reagents but not with organolithium compounds.¹¹ Highly reactive zerovalent palladium catalyst can be directly generated in situ from $\text{PdCl}_2\text{-PPh}_3\text{-CH}_3\text{Li}$. Tetrakis(triphenylphosphine)-palladium can be used alternatively. Grignard reagents undergo the reaction as well with aryl halides. Organolithium compounds require the limited reaction condition under which the elimination of alkenyl halides producing lithium acetylides is slower than the cross-coupling reaction.⁷ The choice of benzene as a solvent and the dilution of the solution satisfy the above conditions. The palladium-catalyzed alkylation of aryl halides with organolithium compounds proceeds efficiently without such difficulty.⁷ Similar reactions with lithium thiolates gave the corresponding alkenyl sulfides.⁷ Representative reactions of organolithium compounds are shown in Table I.

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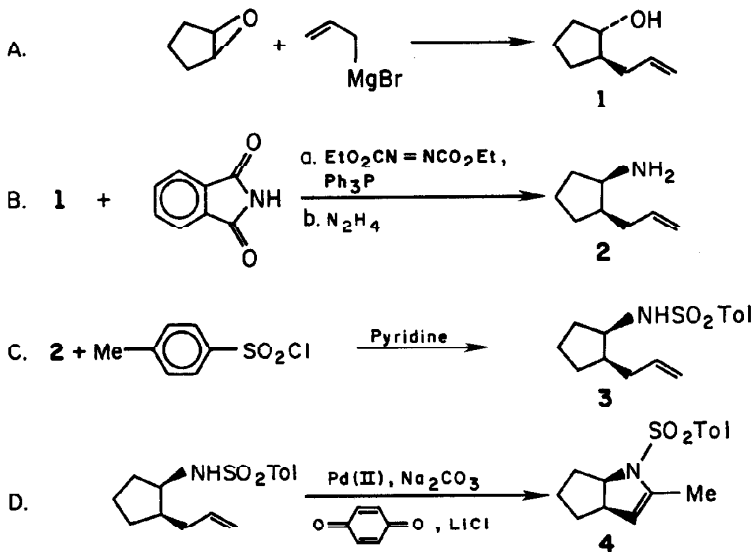
Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

- (Z)- β -[2-(N,N-Dimethylamino)phenyl]styrene: Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)- (9); (70197-43-2)
- (Z)- β -Bromostyrene: Styrene, β -bromo-, (Z)- (8); Benzene, (2-bromoethenyl)-, (Z)- (9); (588-13-8)
- erythro*- α,β -Dibromo- β -phenylpropionic acid: Hydrocinnamic acid, α,β -dibromo-, *erythro*- (8); Benzenepropanoic acid, α,β -dibromo-, (R^* , S^*)- (9); (31357-31-0)
- trans*-Cinnamic acid: Cinnamic acid, (E)- (8); 2-Propenoic acid, 3-phenyl-, (E)- (9); (140-10-3)
- Sodium azide (8,9); (26628-22-8)
- 2-(N,N-Dimethylamino)phenyllithium: Lithium, [o-dimethylamino)phenyl]- (8); Lithium, [2-(dimethylamino)phenyl]- (9); (22608-37-3)
- N,N-Dimethylaniline: Aniline, N,N-dimethyl- (8); Benzenamine, N,N-dimethyl- (9); (121-69-7)
- Butyllithium: Lithium, butyl- (8,9); (109-72-8)
- Palladium chloride (8,9); (7647-10-1)
- Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)
- Methyllithium: Lithium, methyl- (8,9); (917-54-4)

cis-N-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE
(Cyclopenta[b]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-
1-[4-methylphenyl)sulfonyl]-, cis-)



Submitted by Louis S. Hegedus, Michael S. Holden, and James M. McKearin¹.
 Checked by Christoph Nübling and Ian Fleming.

1. Procedure

A. *trans*-8-(3-Propenyl)cyclopentanol. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser with a stopcock, and a 250-mL addition funnel is charged with 18.3 g (750 mmol) of magnesium turnings (Note 1). The system is evacuated and placed under argon. then 100 mL of ethyl ether (Note 2) is added to the system via cannula. The system is placed in an ice-water bath, and 2 mL of allyl bromide (Note 3) is added via syringe to the magnesium suspension to initiate Grignard formation. The addition funnel is charged with 45.5 g (375 mmol) of allyl bromide and 30 mL of ethyl ether. Another 100 mL of ethyl ether is added to the reaction flask. Stirring is begun, and the allyl bromide-ethyl ether mixture is added dropwise to the cooled reaction flask over a period of about 2 hr. After the addition is complete, the dark gray solution is stirred for several hours at ambient temperature (Note 4). Meanwhile, a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser with a stopcock, and a 60-mL addition funnel is evacuated and placed under argon. The Grignard solution is transferred, via cannula, into the flask, and 16.8 g (200 mmol) of cyclopentene oxide (Note 5) is placed in the addition funnel. While the solution is stirred, the epoxide is added dropwise to the Grignard reagent at a rate sufficient to maintain a mild reflux. After the solution is stirred for several hours or overnight, the flask containing the dark gray reaction mixture is placed in an ice-water bath, and excess Grignard reagent is hydrolyzed with 40 mL of a saturated aqueous ammonium chloride solution. The fine white precipitate is allowed to settle (Note 6), and the liquid is decanted into a 500-mL separatory funnel. The precipitate is washed with ethyl ether (4 x 50 mL) (Note 7), and all the ethyl ether solutions are

combined, washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL), then with saturated aqueous sodium chloride (2 x 20 mL). The aqueous layers are combined and washed with ethyl ether (2 x 20 mL). The ether layers are combined and dried over anhydrous potassium carbonate. The desiccant is removed by gravity filtration, and the solvent removed under reduced pressure to give 24.1-26.4 g (96-105%) of a yellow oil. Distillation (43°C, 0.250 mm) yields 1 (19.8-23.0 g, 78-91%) as a clear, colorless oil (Note 8).

B. *cis*-2-(2-Propenyl)cyclopentylamine. A 1000-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two addition funnels, and a stopcock is charged with 41.5 g (158 mmol) of triphenylphosphine (Note 9) and 23.3 g (158 mmol) of phthalimide (Note 10). The system is evacuated and placed under argon. To one addition funnel, 20.0 g (158 mmol) of trans-2-(2-propenyl)cyclopentanol is added; 27.5 g (158 mmol) of diethyl azodicarboxylate (Note 11) is added to the other. Tetrahydrofuran, 500 mL, (Note 12) is added to the flask via cannula, and stirring is begun. The substrate and diethyl azodicarboxylate are simultaneously added dropwise, slowly over about 30 min (Note 13), with stirring; the solution turns clear and yellow (Note 14). The reaction is permitted to proceed for 2 days at room temperature; the solution is then transferred to a 1000-mL, one-necked, round-bottomed flask, and the solvent is removed under reduced pressure, to leave a yellow-white semi-solid. A magnetic stirring bar is added to the flask and the semi-solid is taken up in 250 mL of reagent-grade methyl alcohol. To this, 10.1 g (316 mmol) of hydrazine (Note 15) is added. A reflux condenser is attached to the flask, stirring is begun, and the system is brought to reflux (Note 16). A large amount of clumpy white solid forms in a yellow-to-orange solution. After 4 hr at reflux, the solution is allowed to cool to room temperature; a mixture of 20 mL of hydrochloric acid (Note 17) and 65 mL of methyl alcohol is

added, and the system is refluxed overnight. The resulting reaction mixture is filtered to remove the precipitate, and the solvent is removed under reduced pressure to yield a white-to-pink solid, which is taken up in 800 mL of water and 28 mL of hydrochloric acid. The solution is filtered, and the solid washed with water (2 x 200 mL) and hydrochloric acid (20 mL). The liquids are combined, placed in a 2000-mL separatory funnel, and washed with chloroform (3 x 250 mL), and ethyl ether (1 x 250 mL). The aqueous layer is transferred to a 2000-mL Erlenmeyer flask, and cooled in an ice-water bath. A saturated aqueous sodium hydroxide solution is used to make the solution basic, to approximately pH 14, whereupon the solution turns dark olive green. The basic solution is extracted with ethyl ether (10 x 250 mL), or by continuous extraction overnight and the combined organic layers are dried over a mixture of anhydrous sodium sulfate and anhydrous potassium carbonate. Filtration and solvent removal at atmospheric pressure yields a green-yellow oil. Distillation (52-58°C, 8-11 mm) gives 2 (11.8-12.5 g, 60-63%) as a clear, colorless oil (Note 18).

C. *cis*-1-*N*-Tosyl-2-(2-propenyl)cyclopentylamine. A 100-mL, one-necked, round-bottomed flask equipped with a sidearm, a magnetic stirring bar, stopcock, and a serum cap on the sidearm, is charged with 8.00 g (64 mmol) of *cis*-2-(2-propenyl)cyclopentylamine. The system is evacuated and placed under argon. Via cannula, 50 mL of pyridine (Note 19) is added. The flask is cooled in an ice-water bath, the stopcock removed, 12.58 g (66 mmol) of *p*-toluenesulfonyl chloride (Note 20) is added to the reaction mixture, and the stopcock replaced. The reaction mixture immediately turns orange; it is allowed to stir at 0°C overnight, during which time the reaction mixture turns deep purple. The reaction mixture is then poured into a separatory funnel, 60 mL of distilled technical grade ethyl acetate is added, and the solution is

washed with 100-mL portions of 1:1 2 N HCl: saturated aqueous sodium chloride until the washings are acidic. The organic layer is washed with saturated aqueous sodium chloride (2 x 60 mL), and dried over anhydrous magnesium sulfate. Gravity filtration and solvent removal under reduced pressure yield a dark red-brown solid. This is purified by recrystallization from 250 mL of ethyl alcohol/water (4:1); crystallization is completed in the refrigerator to give **3** (12.7-13.9 g, 71-78%) as off-white plates, mp 109-110°C (Note 21).

D. *cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene*. A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser is charged with 5.159 g (18.49 mmol) of *cis*-1-N-tosyl-2-(2-propenyl)cyclopentylamine, 1.998 g (18.49 mmol) of *p*-benzoquinone (Note 22), 0.096 g (0.370 mmol, 2 mole-%) of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (Note 23), 3.920 g (92.46 mmol, 500 mole-%) of lithium chloride (Note 24), and 1.960 g (18.49 mmol) of sodium carbonate (Note 25). Tetrahydrofuran (100 mL) (Note 12) is added and stirring is begun. The yellow-orange solution is heated at reflux until thin-layer chromatography (3:1 hexane:ethyl acetate, SiO_2) shows that no starting material remains (about 3-4 hr); it is then poured into a 500-mL separatory funnel and 100 mL of ethyl acetate is added. This is washed with 100-mL portions of 1:1 saturated aqueous sodium chloride: sodium hydroxide (1%) until the aqueous layer is clear; then the yellow-green organic layer is washed with saturated aqueous sodium chloride (2 x 50 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered by gravity, passed through a short column (approximately 5 cm) of neutral alumina, and the column is washed with 100 mL of ethyl acetate. The combined solvents are removed under reduced pressure to give 4.9-5.1 g (94-99%) of a tan solid. The product is recrystallized from 100 mL of methyl alcohol/water (4:1) to yield **4** (3.9-4.45 g, 76-87%) as white needles, mp 91-92°C (Notes 26 and 27).

2. Notes

1. Magnesium turnings, purified for Grignard reactions, are purchased from J. T. Baker Chemical Company, and used without further purification.
2. Ethyl ether is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
3. Allyl bromide, purchased from Aldrich Chemical Company, Inc., is distilled and stored in a brown bottle away from light.
4. Successful reactions have been run with this induction period lasting from 1 hr to overnight.
5. Cyclopentene oxide is purchased from Arapahoe Chemicals, Boulder, CO, and used without purification. The checkers bought cyclopentene oxide from Lancaster Synthesis.
6. The fine precipitate may take several hours to settle. Filtration is often ineffective, but settling can be speeded up by centrifuging.
7. Since the efficiency of this washing is dependent upon the degree of settling, the checkers recommend that washing with 50-mL batches of ether be continued until the smell of the alcohol is no longer detectable on a sample of the dry salts.
8. The spectral properties are as follows: ^1H NMR (CDCl_3) δ : 1.0-2.4 (m, 9 H); 3.0-3.3 (br s, 1 H, O-H); 3.7-4.1 (m, 1 H, CH-O); 4.8-5.3 (m, 2 H, $=\text{CH}_2$); 5.5-6.2 (m, 1 H, $-\text{CH}=\text{}$).
9. Anhydrous triphenylphosphine is purchased from Sigma Chemical Company, and is used without further purification.
10. Phthalimide, 98%, is purchased from Aldrich Chemical Company, Inc., and is used without further purification.

11. Diethyl azodicarboxylate is purchased from Aldrich Chemical Company, Inc., and is used without further purification.
12. Tetrahydrofuran is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.
13. Too rapid a rate of addition may cause the solution to boil.
14. The solution does not become homogeneous until it is warmed by the heat of the reaction.
15. Anhydrous hydrazine, 97+%, is purchased from Matheson, Coleman and Bell, Norwood, OH 45212, and is used without further purification.
16. Because of the dangerous nature of hydrazine, a safety shield should always be in place during this reaction.
17. A.C.S. Reagent hydrochloric acid is purchased from Fisher Scientific Company, and used without further purification.
18. The spectral properties are as follows: ^1H NMR (CDCl_3) δ : 0.8 (s, 2 H, NH_2); 1.3-2.4 (m, 9 H, CH_2 , CH); 3.1-3.4 (m, 1 H, HC-N); 4.8-5.2 (m, 2 H, $=\text{CH}_2$); 5.4-6.1 (m, 1 H, HC=).
19. Pyridine is distilled from CaH_2 and stored over CaH_2 under argon.
20. p-Toluenesulfonyl chloride is purchased from J. T. Baker Chemical Company, and purified by dissolving 20 g in 50 mL of chloroform, adding 250 mL of hexane, filtering, and solvent removal under reduced pressure.²
21. The spectral properties are as follows: ^1H NMR (CDCl_3) δ : 1.0-2.3 (m, 9 H, CH_2 , CH); 2.41 (s, 3 H, CH_3); 3.4-3.8 (m, 1 H, CHN); 4.7-5.1 (m, 3 H, $=\text{CH}_2$, NH); 5.2-6.1 (m, 1 H, $=\text{CH}$); 7.25 (d, 2 H, $J = 8$, ArH); 7.8 (d, 2 H, $J = 8$, ArH).
22. p-Benzoquinone, 98+%, is purchased from the Aldrich Chemical Company, Inc., sublimed at $60^\circ\text{C}/15$ mm, and stored under argon. The checkers used it as supplied.

23. Palladium(II) chloride-acetonitrile complex is formed by placing 8.00 g of PdCl_2 in 200 mL of acetonitrile and stirring for 2 days or refluxing for 3 hr. The complex (11.43 g, 97.8%) is collected by filtration, washed, and dried.

24. Lithium chloride is purchased from Fisher Scientific Company and used without further purification.

25. Sodium carbonate is purchased from Aldrich Chemical Company, Inc., and used without further purification.

26. The spectral properties are as follows: ^1H NMR (CDCl_3) δ : 1.40-2.00 (m, 6 H, CH_2); 2.10 (m, 3 H, $\text{CH}_3\text{C=}$); 2.40 (s, 3 H, ArCH_3); 2.80-3.20 (m, 1 H, 4.20-4.50 (m, 1 H, CHN); 4.70 (m, 1 H, CH-); 7.30 (d, 2 H, $J = 0$, ArII); 7.70 (d, 2 H, $J = 8$, ArH).

27. The checkers also carried out the entire sequence on three times the scale with slightly better yields.

3. Discussion

Synthesis of the title compound is representative of a number of syntheses of nonaromatic nitrogen heterocycles via Pd(II)-catalyzed amination of olefins.³ These tosylated enamines are not readily available by standard synthetic methods, and show potential for further functionalization of the heterocycle.⁴ The saturated amine can be synthesized from the title compound by hydrogenation of the double bond followed by photolytic deprotection.³

In terms of cost, the effectiveness of the catalytic cycle in the ring closure makes this process economical in palladium. The first three steps in the reaction sequence -- ring opening of an epoxide by a Grignard reagent,⁵ conversion of an alcohol to an amine with inversion,⁶ and sulfonamide formation from the amine⁷ -- are all standard synthetic processes.

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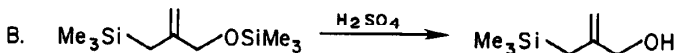
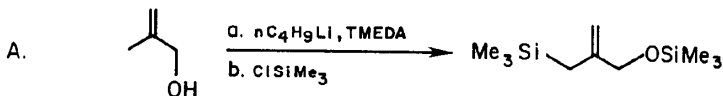
Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

- cis-N-Tosyl-3-methyl-2-azabicyclo[3.3.0]oct-3-ene: Cyclopenta[b]pyrrole, 1,3a,4,5,6,6a-hexahydro-2-methyl-1-[(4-methylphenyl)sulfonyl]-, cis- (11); (81097-07-6)
- trans-2-(2-Propenyl)cyclopentanol: Cyclopentanol, 2-(2-propenyl)-, trans- (10); (74743-89-8)
- Magnesium (8,9); (7439-95-4)
- Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)
- Cyclopentene oxide: 6-Oxabicyclo[3.1.0]hexane (8,9); (285-67-6)
- cis-2-(2-Propenyl)cyclopentylamine: Cyclopentanamine, 2-(2-propenyl)-, cis- (11); (81097-02-1)
- Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)
- Phthalimide (8); 1 H-Isoindole-1,3(2H)-dione (9); (85-41-6)
- Diethyl azodicarboxylate: Formic acid, azodi-, diethyl ester (8);
- Diazenedicarboxylic acid, diethyl ester (9); (1972-28-7)
- Hydrazine (8,9); (302-01-2)
- cis-1-N-Tosyl-2-(2-propenyl)cyclopentylamine: Benzenesulfonamide, 4-methyl-N-[2-(2-propenyl)cyclopentyl]-, cis- (11); (81097-06-5)
- p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)
- p-Benzoquinone: Benzoquinone (8); 2,5-Cyclohexadiene-1,4-dione (9); (106-51-4)
- Palladium(II) chloride: Palladium chloride (8,9); (7647-10-1)

**SILYLATION OF 2-METHYL-2-PROPEN-1-OL DIANION:
2-(HYDROXYMETHYL)ALLYLTRIMETHYLSILANE**



Submitted by Barry M. Trost, Dominic M. T. Chan, and Thomas N. Nanninga¹.

Checked by Paul R. Jenkins and Ian Fleming.

1. Procedure

Caution! Part A should be carried out in an efficient hood, since the reagents are noxious.

A. *2-(Trimethylsiloxy)allyltrimethylsilane.* An oven-dried (Note 1) 2-L, three-necked, round-bottomed flask is equipped with an air-tight mechanical stirrer (Note 2), a 500-mL pressure-equalizing dropping funnel (Note 3), and a reflux condenser. The top of the condenser is connected to a three-way stopcock with one branch connected to a nitrogen source and the other to a variable pressure oil pump with a dry-ice trap (Note 4). The apparatus is flamed dry under a steady stream of nitrogen. The flask is

charged with 836 mL (1.07 mol) of a 1.28 M solution of n-butyllithium in hexane (Note 5). The bulk of the hexane is removed at reduced pressure with stirring until a thick oil is obtained (Note 6). The system is carefully recharged with nitrogen. The n-butyllithium is then cooled in an ice bath and 500 mL of anhydrous ether is added (Note 7), followed by 160 mL of tetramethylethylenediamine (Note 8). The mixture is stirred for a few minutes and 34 mL, 29.14 g (0.404 mol) of 2-methyl-2-propen-1-ol (Note 9) is added dropwise via a syringe over 22 min (Note 10). An immediate, vigorous reaction occurs and the lithium alkoxide precipitates as a white solid. Approximately 350 mL of tetrahydrofuran (Note 11) is added and the resultant slightly cloudy yellow solution is allowed to warm to room temperature over ca. 4 hr (Note 12). The reaction is stirred for 39 hr (Note 13) at which time the dianion separates as a dark red gummy material from the deep orange solution. The mixture is cooled to ca. -30°C (Note 14) and 230 mL (1.81 mol) of chlorotrimethylsilane (Note 15) is added all at once over ca. 20 sec. The reaction turns milky white (Note 16). After 5 min, the dry ice bath is removed and the mixture is stirred for a further 15 min at room temperature. The reaction mixture is added in two portions with swirling to 1.5 L of ether in two 2-L conical flasks, after which 1 L of saturated aqueous sodium bicarbonate is added very carefully to destroy excess chlorotrimethylsilane (Note 17). The two layers are separated and the aqueous phase is extracted with a further 1.5 L of ether. The combined organic layer is then washed with 1 L of water, two 1-L portions of saturated aqueous copper sulfate solution and 400 mL of water. The solution is dried over anhydrous potassium carbonate and the solvent is removed by atmospheric distillation (Note 18). Careful distillation of the residual oil through a 27-cm Vigreux column at reduced pressure

gives a forerun of 4.25 g, bp 29-57°C (4 mm), and 45.8 g (52%) of 2-(trimethylsiloxy)allyltrimethylsilane as a colorless liquid, bp 57-59°C (4 mm) (Note 19).

B. *2-(Hydroxymethyl)allyltrimethylsilane*. A 500-mL round-bottomed flask equipped with a magnetic stirring bar is charged with 21.10 g (0.0975 mol) of 2-(trimethylsiloxyethyl)allyltrimethylsilane in 170 mL of tetrahydrofuran (Note 11) and 44 mL of ca. 1 N aqueous sulfuric acid (Note 20). The resultant two-phase mixture is then stirred vigorously for 1.5 hr at room temperature. Solid anhydrous potassium carbonate is added carefully until bubbling subsides. The layers are separated and the aqueous layer is extracted with 100 mL of ether. The combined organic layers are dried over anhydrous potassium carbonate and distilled at atmospheric pressure to remove the solvents (Note 18). The remaining liquid is distilled at reduced pressure to give a forerun, 0.4 g, bp 22-54°C (4 mm), and 10.95 g (78%) of 2-(hydroxymethyl)-allyltrimethylsilane as a colorless liquid, bp 54-56°C (2 mm) (Note 21).

2. Notes

1. All glassware was dried in an oven at over 100°C overnight.
2. The use of a magnetic stirrer is not advisable since the formation of the gum-like dianion prevents efficient stirring. A mechanical stirrer with a ground-glass shaft bearing lubricated with mineral oil is recommended.
3. The funnel is capped with a rubber septum. For ease of operation, volume markings, corresponding to the amounts of reagents to be added, are put on the addition funnel.

4. The function of the trap is to condense the hexane from the n-butyllithium solution. The checkers used a 1-L three-necked flask fitted with a short delivery tube (a quick fit air bleed tube was used), stopper, and rubber tubing connection. The submitters used a water aspirator and a 1-L filter flask with a drying tower between.

5. n-Butyllithium in hexane was purchased by the checkers from Pfizer Chemicals Ltd., UK, and manufactured by the Lithium Corporation of America. It was titrated using the double titration method with dibromoethane and transferred to the addition funnel using a cannula. The submitters used a 1.58 M solution from the Foote Mineral Company; they found that the yield of product was reduced to ca. 42% when only two equivalents of the lithium reagent were used.

6. One should try to remove as much hexane as possible from the n-butyllithium solution (i.e. greater than 90%) because the purity of the product depends on the polarity of the reaction medium. A warm water bath was used to facilitate solvent removal. The checkers used a variable pressure oil pump with the vacuum adjusted to ca. 10-20 mm.

7. Ether was distilled from sodium ketyl of benzophenone. The dissolution of n-butyllithium in ether was slightly exothermic.

8. Tetramethylethylenediamine was obtained from Aldrich Chemical Company and distilled from calcium hydride before use.

9. 2-Methyl-2-propen-1-ol, purchased from Aldrich Chemical Company, was distilled from anhydrous potassium carbonate. It was added directly to the n-butyllithium solution using a long needle. The checkers quickly replaced the pressure-equalizing dropping funnel with a serum cap to carry out this addition. The funnel was fitted to a small dry flask to prevent the introduction of moisture during the addition period and replaced on the reaction flask immediately afterwards.

10. The reaction of the alcohol with *n*-butyllithium is quite vigorous with evolution of butane.

11. Tetrahydrofuran was distilled from sodium ketyl of benzophenone.

12. The checkers renewed the ice bath when additions were complete and allowed the flask to remain in the ice bath without addition of fresh ice.

13. Dianion formation appears to be essentially complete within 24 hr. However, a reaction time of 36 hr is recommended by the submitters to ensure complete reaction.

14. An extremely violent reaction is observed if the dianion is quenched above 0°C, with ether boiling off at an uncontrollable rate. The submitters observed that if the chlorotrimethylsilane addition is performed at a lower temperature, the reaction temperature will remain below that of the boiling point of ether. A dry-ice bath made up of 80:20 (v/v) ethanol-water was used; the checkers measured a bath temperature of -55°C and kept the reaction in the bath for 15 min before adding chlorotrimethylsilane.

15. Chlorotrimethylsilane was distilled from tributylamine before use. Both of these reagents were obtained from the Aldrich Chemical Company.

16. The submitters observed the appearance of a brown color at this point. The checkers obtained a brown color only after the reaction mixture was added to ether. In a run at half scale the reaction mixture remained milky white for 35 min and turned brown only when ether (500 mL) was added to it.

17. The submitters observed more precipitate on dilution with ether and recommended that the aqueous workup be performed in a hood.

18. The submitters distilled most of the solvent using a bath temperature increasing up to 100°C. The checkers used a rotary evaporator with a hot water bath.

19. A variable pressure oil pump was used in this distillation. Approximately 10 g of a volatile component, consisting mostly of hexamethyldisiloxane, was obtained at room temperature (15 mm) before the forerun. The forerun contained the desired product and mineral oil from the *n*-butyllithium solution. The pot residue was about 5 g. The submitters find the disilyl compound thus obtained is contaminated with a trace amount of mineral oil and 4-6% of a vinylsilane, probably 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene. This impurity becomes quite significant if the reaction medium is less polar than the one described (e.g., too much hexane from *n*-butyllithium is allowed to remain behind). The spectral properties of the desired product determined by the checkers are as follows: IR (neat) cm^{-1} : 2955, 1643, 1636, 1250, 1085, 885-830; ^1H NMR (chloroform-*d*, 90 MHz) δ : 0.03 (s, 9 H, $\text{CH}_2\text{Si}(\text{CH}_3)_3$), 0.14 (s, 9 H, $\text{OSi}(\text{CH}_3)_3$), 1.50 (broad s, 2 H, $\text{CH}_2\text{-Si}(\text{CH}_3)_3$), 3.93 (broad s, 2 H, $\text{CH}_2\text{-OSi}(\text{CH}_3)_3$), 4.62 (m, 1 H, vinyl H), 4.92 (m, 1 H, vinyl H).

The checkers observed small NMR peaks assigned to mineral oil at δ 0.9 and 1.28 and peaks assigned to 2-methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene at δ 1.87 and 4.1. When the reaction was carried out at half scale the quantity of the latter impurity was not measurable from the NMR integral; however, a run at full scale gave about 10% of the impurity as estimated from the NMR integral. The product from the run at half scale had bp 56-57°C (2 mm), submitters bp 65°C (5.5 mm).

20. The acid solution was prepared by adding 13.5 mL of concentrated sulfuric acid to 500 mL of distilled water.

21. A variable pressure pump is used for the distillation. The forerun consisted of mineral oil contaminant and product. The allylic alcohol is not very stable at room temperature but can be kept indefinitely in the refrig-

methylenecyclopentanes via the trimethylenemethane-palladium complex.⁴ This cycloaddition has served as a key step in synthetic approaches directed toward natural products such as brefeldin A⁶ and albene.⁷

The present procedure provides a convenient two-step route to 2-(hydroxymethyl)allyltrimethylsilane using relatively inexpensive reagents. Other approaches require more steps and expensive chloromethyltrimethylsilane.^{3,8}

Dianion formation from 2-methyl-2-propen-1-ol seems to be highly dependent on reaction conditions. Silylation of the dianion generated using a previously reported method⁹ was unsuccessful in our hands. The procedure described here for the metalation of the allylic alcohol is a modification of the one reported for formation of the dianion of 3-methyl-3-buten-1-ol.¹⁰ The critical variant appears to be the polarity of the reaction medium. In solvents such as ether and hexane, substantial amounts (15-50%) of the vinylsilane 3 are observed. Very poor yields of the desired product were obtained in dimethoxyethane and hexamethylphosphoric triamide, presumably because of the decomposition of these solvents under these conditions. Empirically, the optimal solvent seems to be a mixture of ether and tetrahydrofuran in a ratio (v/v) varying from 1.4 to 2.2; in this case 3 becomes a very minor component.

A similar procedure has been employed to silylate the dianion of 3-methyl-3-buten-2-ol (67% yield).¹¹ In systems where such internal activation is not possible (e.g. 2-methyl-2-cyclohexen-1-ol), dianion formation can be performed in hexane to give a 75% yield of the corresponding disilyl compound.¹²

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

n-Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Tetramethylethylenediamine: Ethylenediamine, N,N,N',N'-tetramethyl- (8);

1,2-Ethanediamine, N,N,N',N'-tetramethyl- (9); (110-18-9)

2-Methyl-2-propen-1-ol: 2-Propen-1-ol, 2-methyl- (8,9); (513-42-8)

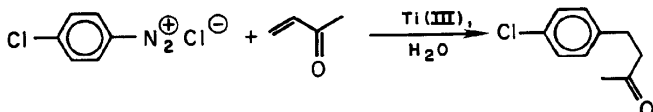
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

2-(Acetoxymethyl)allyltrimethylsilane: 2-Propen-1-ol, 2-[(trimethylsilyl)-methyl]-, acetate (10); (72047-94-0)

REDUCTIVE ARLATION OF ELECTRON-DEFICIENT OLEFINS:

4-(4-CHLOROPHENYL)BUTAN-2-ONE

(2-Butanone, 4-(4-chlorophenyl)-)



Submitted by Attilio Citterio.

Checked by Robert Haessig, Len Widler, and Dieter Seebach.

1. Procedure

Caution! Like all vinyl monomers, 3-buten-2-one is toxic and the preparation should be carried out in a well-ventilated hood.

A 500-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a gas inlet, an externally cooled, pressure-equalizing dropping funnel (Note 1), and a gas bubbler is charged with 15% aqueous titanium trichloride (92 mL, 0.109 mol) (Note 2). N,N-Dimethylformamide (Note 3) (70 mL) is added during 45 min with stirring and cooling (ice-bath; 0-5°C) while nitrogen is bubbled through the solution. Freshly distilled 3-buten-2-one (5.7 mL, 0.066 mol) is added at 0-5°C by syringe. The nitrogen flow is stopped, and 4-chlorobenzenediazonium chloride solution (0.044 mol) (Note 4) is added dropwise at 0-5°C from the dropping funnel. After 2-3 min, nitrogen evolution commences, and the rate of addition is

adjusted so that 1-2 bubbles/sec are vented through the bubbler. Nitrogen evolution continues for 20 min after the addition is complete (1.5 hr). The ice-bath is removed and the solution stirred for 1 hr at room temperature. Ether, 50 mL, is added with stirring, and the organic phase is separated. The aqueous phase is extracted with ether (3 x 50 mL) and the combined organic extracts are washed with 3% aqueous Na_2CO_3 (2 x 30 mL) and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is distilled to give 5.2-6.0 g (65-75% yield) of 4-(4-chlorophenyl)butan-2-one as a pale-yellow liquid, bp 90-91°C (0.5 mm) (Note 5).

2. Notes

1. The checkers used a dropping funnel with temperature-control jacket (Normag N 8055, Otto Fritz GmbH, Normschliff-Aufbaugeräte (Normag), D-6238 Hofheim am Taunus).

2. The 15% titanium trichloride solution was purchased from Carlo Erba Chemicals or from Merck & Company, Inc., but can also be prepared by dissolving metallic titanium in 20% aqueous hydrochloric acid² or by dissolving solid titanium trichloride in 1 M aqueous hydrochloric acid. Titanium(III) sulfate (from BDH Chemicals Ltd.) can also be used. All titanium(III) solutions were titrated with aqueous cerium(IV) sulfate prior to use.

3. N,N-Dimethylformamide from Carlo Erba Chemicals, from Fluka AG, or from Merck & Company, Inc. was used as received. Other solvents (for example, acetone, acetic acid, acetonitrile) can also be used.

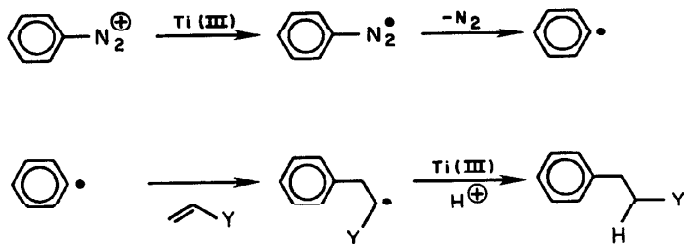
4. The 4-chlorobenzenediazonium chloride solution is prepared as follows: finely powdered 4-chloroaniline (5.65 g, 0.044 mol) is suspended in 18 mL of 24% aqueous hydrochloric acid and cooled to 0°C. Sodium nitrite (3.2 g, 0.046 mol) in water (7 mL) is added dropwise during 45 min at 0-5°C to give a pale yellow solution of the diazonium salt.

5. The physical properties of the product are as follows: n_D^{25} 1.5251; IR (liquid film) cm^{-1} : 1715; ^1H NMR (CDCl_3) δ : 2.0 (s, 3 H), 2.6-2.8 (m, 4 H), 6.8-7.3 (m, 4 H); mass spectrum m/e : 182 (M); semicarbazone, mp 165°C (164-165.5°C⁴). GLC analysis (glass capillary column, 20 m, pluronic L-64, program: 120-200°C at 5°C/min): >99% pure.

3. Discussion

This synthesis is only one example of a wide range of reactions which involve aryl (or alkyl) radical addition to electron-deficient double bonds resulting in reduction.^{3,5,6} The corresponding oxidative reaction using aryl radicals is the well known Meerwein reaction,⁷ which uses copper(II) salts.

General arylation reactions are summarized by the following equations and some specific examples are presented in Table I.



Homolytic cleavage of diazonium salts to produce aryl radicals is induced by titanium(III) salt, which is also effective in reducing the α -carbonylalkyl radical adduct to olefins, telomerization of methyl vinyl ketone, and dimerization of the adduct radicals. The reaction can be used with other electron-deficient olefins, but telomerization or dimerization are important side reactions.

Other limitations of the reaction are related to the regioselectivity of the aryl radical addition to double bond, which is mainly determined by steric and radical delocalization effects.⁸ Thus, methyl vinyl ketone gives the best results, and lower yields are observed when bulky substituents are present in the β -position of the alkene. However, the method represents complete positional selectivity because only the β -adduct radicals give reductive arylation products whereas the α -adduct radicals add to diazonium salts, because of the different nucleophilic character of the alkyl radical adduct.^{8,9}

The product described here, 4-(4-chlorophenyl)butan-2-one, was previously prepared in the following ways: a) by reduction of the corresponding benzalacetone,¹⁰ b) by catalyzed decarbonylation of 4-chlorophenylacetaldehyde by $\text{HFe}(\text{CO})_4$ in the presence of 2,4-pentanedione,¹¹ c) by reaction of 4-chlorobenzyl chloride with 2,4-pentanedione under basic catalysis (K_2CO_3 in EtOH),⁴ d) by reaction of 4-chlorobenzyl chloride with ethyl 3-oxobutanoate under basic catalysis (LiOH),¹² and e) by reaction of 3-(4-chlorophenyl)-propanoic acid with methyl lithium.¹³

TABLE I

REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS BY ARENEDIAZONIUM
SALTS INDUCED BY TITANIUM(III) SALTS

				yield ^a
X	R	R'	Y	(%)
4-OCH ₃	H	H	COCH ₃	65
H	H	H	COCH ₃	75
4-Br	H	H	COCH ₃	68
4-COCH ₃	H	H	COCH ₃	72
4-Cl	H	H	CHO	63
4-Cl	CH ₃	H	COCH ₃	44
4-Cl	CH(CH ₃) ₂	H	COCH ₃	28
4-Cl	C(CH ₃) ₃	H	COCH ₃	14
4-Cl	CH ₃	CH ₃	COCH ₃	12
4-Cl	Ph	H	COCH ₃	18
4-Cl	H	H	CN	25 ^b
4-Cl	H	H	COOH	33 ^b
4-Cl	H	H	COOEt	32 ^b

^aFrom the diazonium salt. ^b Telomers are formed; the reactions are carried out with twice the amount of titanium(III) salt.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-(4-Chlorophenyl)butan-2-one: 2-Butanone, 4-(p-chlorophenyl)- (8);

2-Butanone, 4-(4-chlorophenyl)- (9); (3506-75-0)

3-Buten-2-one (8,9); (78-94-4)

Titanium trichloride: Titanium chloride (8,9); (7705-07-9)

SELECTIVE HALOGEN-LITHIUM EXCHANGE REACTIONS

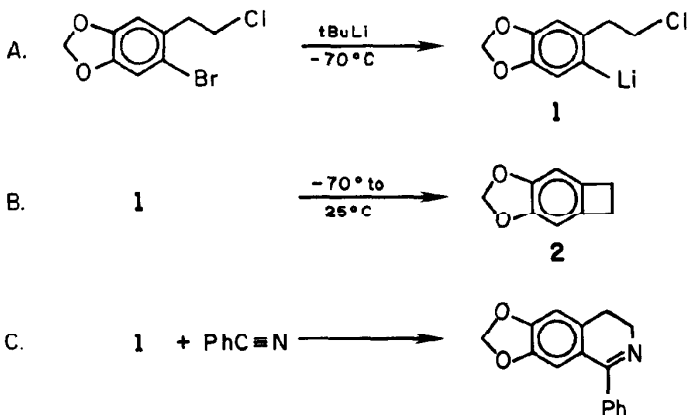
OF 2-(2'-HALOPHENYL)ETHYL HALIDES:

SYNTHESIS OF 4,5-METHYLENEDIOXYBENZOCYCLOBUTENE AND

1-PHENYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE

(Cyclobuta[*f*]-1,3-benzodioxole, 5,6-dihydro- and

1,3-dioxolo[4,5-*g*]isoquinoline, 7,8-dihydro-5-phenyl-)



Submitted by Dennis J. Jakiela, Paul Helquist,¹ and Lawrence D. Jones².

Checked by Neville D. Emslie and Ian Fleming.

1. Procedure

A. *2-(2'-Lithio-4',5'-methylenedioxyphenyl)ethyl chloride*. A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel (Note 1), low temperature thermometer, and a three-way stopcock having a vertically-oriented tube capped with a rubber septum and a horizontal tube connected to a source of dry nitrogen and vacuum, is charged with 10.0 g (37.9 mmol) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethyl chloride (Note 2). The assembled apparatus is evacuated and refilled with nitrogen three times. Freshly distilled diethyl ether (200 mL) (Note 3) is added to the flask by means of a double-ended needle (0.5 m in length) inserted through the vertical tube of the stopcock while a slight vacuum is applied to the apparatus. A slightly positive pressure of nitrogen is then maintained in the apparatus throughout the course of the reaction. The solution is cooled in a dry ice-acetone bath (Note 4). The glass jacket (or styrofoam cup) (Note 1), which surrounds the addition funnel, is filled with powdered dry ice, and 33 mL of a 2.3 M solution of tert-butyllithium (76 mmol) in pentane (Note 5) is added to the addition funnel by means of a syringe. After 10 min the lithium reagent is added dropwise to the flask over a period of 1 hr, while the temperature of the reaction mixture is maintained below -60°C. The solution of the resulting aryllithium reagent 1 is then used in either of the two reactions described below.

B. *4,6-Methylenedioxybenzoic acid*. The reaction mixture from Part A is simply allowed to warm to room temperature over a period of several hours, during which time a white precipitate forms. After 18 hr, 100 mL of water is slowly added and the mixture is transferred to a 500-mL separatory funnel. As the mixture is shaken, the solid dissolves in the aqueous phase, which becomes

light brown. The aqueous layer is extracted with two 75-mL portions of diethyl ether, and the combined organic layers are reduced in volume to 150 mL by rotary evaporation, washed with 75 mL of water and then 75 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to dryness by rotary evaporation to give 5.6 g of pale yellow solid (Note 6). This crude product is transferred to a large, dry ice-cooled sublimation apparatus (Note 7) and sublimed over a 6 hr period at 35°C (0.07 mm) at which time a dark brown oil remains in the bottom of the apparatus. The vacuum is released by filling the apparatus with nitrogen, and the cooled portion of the apparatus is allowed to warm to room temperature. Pure 4,5-methylenedioxybenzocyclobutene, 2 (5.1-5.2 g, 91-93%) is obtained as colorless crystals, mp 60-62°C (Note 8).

C. *1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline*. The reaction mixture containing the aryllithium intermediate is stirred for 15 min (internal temperature -65 to -68°C), and then 4.3 mL (42 mmol) of distilled benzonitrile is added quickly. The mixture is allowed to warm gradually to room temperature and the stirring is continued overnight. The yellow solution (Note 9) is diluted with 25 mL of ether, the mixture is poured into a 1-L separatory funnel, and the reaction flask is rinsed with an additional 75 mL of ether. The combined ether solutions are washed with 150 mL of water and then extracted with three 75-mL portions of 10% (w/w) hydrochloric acid. The combined acid extracts are made basic by the addition of 100 mL of 20% (w/w) aqueous sodium hydroxide solution, and the resulting milky white mixture is extracted with three 75-mL portions of dichloromethane. The combined organic extracts are washed with 50 mL of water and 50 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness by rotary evaporation, to give 0.96 g (94% crude yield) of orange-tan solid.

This material is purified by recrystallization from ethyl acetate:acetone 2:1 (v:v) to give a first crop (6.8 g), and by flash chromatography³ of the residue from the mother liquor, using 150 g of 230-400 mesh silica gel (Merck), a 40-mm diameter column, and elution with 10:1 (v:v) ethyl acetate:methanol. A fast moving orange band and a slower moving lemon-yellow band can be clearly seen on the column. The lemon-yellow band is collected from the column and evaporation gives a second crop (1.4 g) of comparably pure material. The total yield of the pale yellow isoquinoline is 8.2 g (86%), mp 135-137°C (Note 10).

2. Notes

1. The checkers used a home-made, glass-jacketed funnel sealed with a rubber septum. The submitters cut one side and part of the bottom of a styrofoam cup and with tape held this in place around the lower part of the addition funnel.

2. This starting material is prepared in three steps from commercially available (from Research Organic/Inorganic Chemical Corp., Belleville, NJ) 3,4-methylenedioxyphenylacetic acid according to well-established procedures that have been applied to similar compounds.⁴ First, 16.0 g (88.8 mmol) of the acid, recrystallized from chloroform, is dissolved in 50 mL of tetrahydrofuran, and the solution is added to a suspension of 5.98 g (158 mmol) of lithium aluminum hydride powder in 225 mL of distilled diethyl ether (Note 3) at 0°C. [Caution: Lithium aluminum hydride is very sensitive to mechanical shock and very reactive towards moisture and other protic substances; its dust is very irritating to skin and mucous membranes. It should not be allowed to come into contact with metallic species or apparatus, including metal

spatulas, because of the potential danger of metal ion-promoted detonation.] The mixture is stirred at 25°C for 16 hr and is then quenched⁵ by the careful, dropwise addition of 6 mL of 15% aqueous sodium hydroxide, and finally 18 mL of water. [Caution: The reaction of excess lithium aluminum hydride with water is very exothermic and produces a large volume of hydrogen gas.] The resulting mixture is stirred for 1 hr and is then subjected to vacuum filtration. The white solid which is retained is washed with three 50-mL portions of diethyl ether, and the combined filtrates are concentrated by rotary evaporation to give 13.1 g (89%) of 2-(3',4'-methylenedioxyphenyl)-ethanol as a clear, yellow oil, bp 136-140°C (0.003 mm). Next, 12.7 g (76.5 mmol) of this compound and 7.4 mL (91.5 mmol) of pyridine are dissolved in 200 mL of dichloromethane at 0°C, and 4.3 mL (83.9 mmol) of neat bromine is added to the solution over a 4-min period. After the solution has been stirred at 25°C for 16 hr, it is washed with three 50-mL portions of 2N hydrochloric acid, two 50-mL portions of saturated aqueous sodium sulfite, two 50-mL portions of water, and 50 mL of saturated aqueous sodium chloride. The organic layer is then dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to give 18.6 g (99.5%) of yellow solid. Recrystallization from a mixture of 160 mL of hexane and 60 mL of ethyl acetate gives 14.6 g (78%) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethanol as light yellow needles: mp 93-94°C. Finally, 9.95 mL (123 mmol) of distilled pyridine and 8.75 mL (120 mmol) of distilled thionyl chloride are added separately to a solution of 14.4 g (58.8 mmol) of the preceding product and 180 mL of chloroform at 25°C. The mixture is heated at reflux for 18 hr, cooled to 25°C, washed with 40 mL of 1 N hydrochloric acid, 40 mL of 5% aqueous sodium carbonate, two 40-mL portions of water, and 40 mL of saturated aqueous sodium

chloride, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give 14.0 g (90%) of brown crystals. Distillation gives 13.0 g (84%) of an oil (bp 130-134°C at 0.006 mm), which solidifies to give the final product as colorless crystals: $^1\text{H-NMR}$ (CDCl_3) δ : 3.08 (t, 2 H, $J = 6.8$), 3.67 (t, 2 H, $J = 6.8$), 5.95 (s, 2 H), 6.74 (s, 1 H), and 6.98 (s, 1 H); mp 47.0-47.5°C (corrected).

3. Commercially available anhydrous diethyl ether is distilled under nitrogen from a solution of the sodium benzophenone radical anion generated by treating a solution of 10 g of benzophenone and 1 L of ether with 10 g of sodium ribbon until a dark blue or purple color persists.

4. Although the dry ice-acetone bath itself attains a temperature of -78°C, the lowest temperature achieved by the solution within the flask is only -68°C.

5. *Caution: tert-Butyllithium is pyrophoric in air; excess quantities of the reagent in the syringe should be discarded very carefully.* The checkers used the reagent available from Aldrich Chemical Company Ltd., England and standardized it by double titration with ethylene dibromide and hydrochloric acid.⁶

6. The submitters also ran the reaction on smaller scales using from 0.5 g to 5.0 g of starting material and regularly obtained a crude yield at this stage of 98-105%.

7. The sublimation apparatus should have at least a 1-cm separation between the upper surface of the crude solid to be sublimed and the bottom of the cooling surface in order to avoid splattering of the oily residue onto the purified product near the end of the sublimation procedure.

8. The product showed the following spectral properties: $^1\text{H NMR}$ (CDCl_3) δ : 3.00 (s, 4 H), 5.75 (s, 2 H), and 6.50 (s, 2 H).

9. At this stage, the submitters had a brick-red reaction mixture which became yellow on dilution with ether.

10. The product showed the following spectral properties: $^1\text{H-NMR}$ (CDCl_3) δ : 2.67 (t, 2 H, $J = 7.5$), 3.73 (t, 2 H, $J = 7.5$), 5.83 (s, 2 H), 6.63 (s, 2 H), and 7.37 (m, 5 H).

3. Discussion

The halogen-metal exchange reaction was pioneered by Gilman and co-workers⁷ who established that substituted aryl bromides would exchange efficiently with *n*-butyllithium and that the reaction was of synthetic value provided that the substituent was not reactive toward alkyl- or aryllithium reagents. More recently, Parham^{4e,8} and others^{4f,9} further defined the scope and limitations of this reaction by demonstrating that haloarenes substituted with electron-withdrawing (CO_2H , CN , CO_2R) or electron-donating [OR , OCH_2O , $\{\text{CH}_2\}_n\text{X}$, where $\text{X} = \text{Br}$, Cl] functional groups would selectively exchange with alkyllithium reagents at low temperature. While a detailed mechanistic evaluation is not within the scope of this discussion, the halogen-metal exchange reaction has been shown to be reversible and rapid at -75°C and, in the exchange of alkyllithium with a haloarene, the equilibrium reaction favors formation of the lithioarene.^{7,10,11}

As exemplified in the present procedure, the reaction has been optimized and extended in scope; it affords functionalized benzocyclobutenes as well as substituted isoquinolines in high yields. Benzocyclobutenes have been used as intermediates in the synthesis of many naturally occurring alkaloids,¹² steroids,¹³ polycyclic terpenoids,¹⁴ and anthracycline antibiotics.¹⁵ The traditional routes leading to the preparation of benzocyclobutenes have been

reviewed¹⁶ and have involved: (1) Cava's cyclization of o-quinodimethane intermediates (via reaction of sodium iodide with $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-o-xylene), (2) thermal extrusion of sulfur dioxide from 1,3-dihydroisothianaphthene 2,2-dioxide, (3) dehydrogenation of the Diels-Alder adducts of 1,4-butadienes and cyclobutenes, and (4) Wolff rearrangement of α -diazoindanones. More recent methods include: (1) thermal rearrangement of p-tolylcarbene,¹⁷ (2) thermal decomposition of 3-isochromanones,¹² and (3) cobalt-catalyzed cyclizations of acetylenic compounds.¹⁸ Many of these methods for synthesizing functionalized benzocyclobutenes involve (a) multi-step routes, (b) unusual or relatively unavailable starting materials, (c) low overall yields, or (d) special apparatus. The method of halogen-metal exchange demonstrates a high degree of selectivity for formation of the lithioarene intermediate, is broad in scope without loss of procedural simplicity, and provides a high-yield route to benzocyclobutenes of general synthetic utility by direct cyclization of readily available 2-(2'-lithiophenyl)ethyl chlorides.^{4e,f,9b}

The lithioarene intermediate has also been shown to be of use in the synthesis of the isoquinoline ring system. This ring system is common to a variety of natural products which possess useful physiological activity. Several methods have been developed for the synthesis of isoquinolines, the most commonly used routes being the Bischler-Napieralski and the Pictet-Spengler reactions.^{19,20} These methods involve electrophilic, aromatic substitution in the key ring-forming steps with the limitation that best results are obtained only when the aromatic ring bears electron-donating substituents. The present method permits use of substrates either with or without electron-donating groups on the aromatic nucleus since generation of the lithioarene has been shown to be relatively independent of the nature of the substituents.^{8a,d}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4,5-Methylenedioxybenzocyclobutene: Cyclobuta[*f*]-1,3-benzodioxole,
5,6-dihydro- (10); (61099-23-8)

1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline: 1,3-Dioxolo[4,5-*g*]iso-
quinoline, 7,8-dihydro-5-phenyl- (10); (55507-10-3)

3,4-Methylenedioxyphenylacetic acid: Acetic acid, [3,4-(methylene-
dioxy)phenyl]- (8); 1,3-Benzodioxole-5-acetic acid (9); (2861-28-1)

Thionyl chloride (8,9); (7719-09-7)

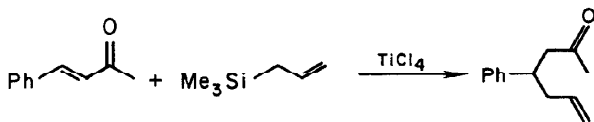
tert-Butyllithium: Lithium, tert-butyl- (8); Lithium, (1,1-dimethylethyl)-
(9); (594-19-4)

Benzonitrile (8,9); (100-47-0)

CONJUGATE ALLYLATION OF α,β -UNSATURATED KETONES WITH ALLYLSILANES:

4-PHENYL-6-HEPTEN-2-ONE

(6-Hepten-2-one, 4-phenyl-)



Submitted by Hideki Sakurai, Akira Hosomi, and Josabro Hayashi¹.

Checked by Todd A. Blumenkopf and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask is fitted with a dropping funnel (Note 1), mechanical stirrer, and reflux condenser attached to a nitrogen inlet. In the flask are placed 29.2 g (0.20 mol) of benzalacetone (Note 2) and 300 mL of dichloromethane (Note 3). The flask is immersed in a dry ice-methanol bath (-40°C) and 22 mL (0.20 mol) of titanium tetrachloride (Note 4) is slowly added by syringe to the stirred mixture. After 5 min, a solution of 30.2 g (0.26 mol) of allyltrimethylsilane (Notes 5 and 6) in 300 mL of dichloromethane is added dropwise with stirring over a 30-min period. The resulting red-violet reaction mixture is stirred for 30 min at -40°C (Note 7), hydrolyzed by addition of 400 mL of H₂O and, after the addition of 500 mL of ethyl ether with stirring, allowed to warm to room temperature. The nearly colorless organic layer is separated and the aqueous layer is extracted with three 500-mL portions of ethyl ether. The organic layer and ether extracts are combined and washed successively with 500 mL of saturated sodium

bicarbonate and 500 mL of saturated sodium chloride, dried over anhydrous sodium sulfate and evaporated at reduced pressure. The residue is distilled under reduced pressure through a 6-inch Vigreux column to give 29.2-30.0 g (78-80%) of 4-phenyl-6-hepten-2-one, bp 69-71°C (0.2 mm), n_D^{20} 1.5156, as a colorless liquid (Note 8).

2. Notes

1. A 500-mL dropping funnel, with pressure-equalizing arm, is used.
2. Benzalacetone is purchased from Wako Pure Chemical Ind., Ltd., or Aldrich Chemical Company, Inc.
3. Dichloromethane is dried over anhydrous calcium chloride, distilled, and stored over 5Å molecular sieves before use. The checkers distilled dichloromethane from calcium hydride immediately before use.
4. Titanium tetrachloride, purchased from Junsei Chemical Co., Ltd., is distilled before use. The checkers purchased titanium tetrachloride from the Fisher Scientific Company, and distilled it from copper powder before use.
5. The starting allyltrimethylsilane can be prepared in satisfactory yield by the procedure of Sommer.² It can also be purchased from PCR Inc., Aldrich Chemical Company, Inc., Fluka A. G., Petrarch Systems Inc., and Tokyo Kasei Kogyo Co., Ltd. The checkers employed material from Petrarch.
6. The use of more than 1.2 equiv of allyltrimethylsilane is essential for shortening the reaction time as well as to avoid contamination of the product by unreacted benzalacetone.
7. Disappearance of benzalacetone and appearance of product can be readily monitored by thin layer or gas chromatographic analysis on a 1-m column packed with 20% Silicone SE-30 at 180°C. The reaction should be stopped as soon as disappearance of benzalacetone is confirmed.

8. Gas chromatographic analysis of the product on a 1-m column packed with 20% Silicone SE-30 at 180°C should give a single peak. The product has the following spectral properties: IR (film) cm^{-1} : 1710, 1630 (C=C); ^1H NMR (CDCl_3) δ : 1.97 (s, 3 H, CH_3CO), 2.35 (t, 2 H, $J = 7.5$, $\text{CH}_2\text{C}=\text{C}$), 2.72 (d, 2 H, $J = 7.5$, CH_2CO), 3.27 (quintet, 1 H, $J = 7.5$, PhCH), 4.8-5.1 (m, 2 H, $\text{CH}_2=\text{C}$), 5.4-5.9 (m, 1 H, $\text{CH}=\text{C}$), 7.0-7.4 (m, 5 H, aromatic).

3. Discussion

This procedure is general for the conjugate allylation of α,β -unsaturated ketones with allylsilanes.³ Some representative examples are listed in Table I. The main advantages of the method are its wide generality and the ready availability of the necessary starting materials. The procedure is often useful for the preparation of δ,ϵ -unsaturated ketones that cannot be obtained in satisfactory yield by the use of allylcuprate (e.g., entry 13) reagents.⁴ Another useful aspect of the reaction is the regiospecific coupling of the allyl group. Examples of this feature can be seen in entries 2 and 5. Although cyclic as well as acyclic α,β -unsaturated ketones give satisfactory results, the reaction is slower in sterically hindered systems (entries 13 and 14). However, even in these cases, good yields are obtained by using excess allylsilane and by conducting the reaction at higher temperature. Since the allyl group can be modified by the regioselective addition of various reagents to the double bond,^{5,6} the method is applicable to the synthesis of a wider variety of compounds than are shown in the Table. By oxidation of the double bond 1,5-diketones may be obtained.⁷ Conjugate allylation with allylsilanes can be used in conjunction with a suitable electrophile to achieve "one-pot" double alkylation at the adjacent vinyl position of an α,β -unsaturated

ketone.⁸ The method has also been utilized in the synthesis of perhydroazulenones.⁹ Allylsilanes also undergo regioselective, Lewis acid-catalyzed reaction with carbonyl compounds,¹⁰ acetals,¹¹ α,β -unsaturated acetals,¹² acyl halides,¹³ tertiary alkyl halides,¹⁴ and oxiranes.¹⁴ Such allylations can also be achieved by using allylstannanes.¹⁵

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TABLE I

CONJUGATE ALLYLATION OF α,β -ENONES WITH ALLYLSILANES PROMOTED BY TITANIUM TETRACHLORIDE^a




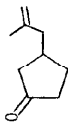
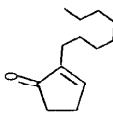
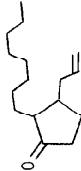
Entry	Allylsilane	Conditions		Temp., °C, time	δ,ϵ -Enone (% yield) ^b
		α,β -Enone			
1	(I) ^c	$\text{CH}_2=\text{CHCOCH}_3$		-78, 1 min	$\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{COCH}_3$ (59)
2	(II) ^d	$\text{CH}_2=\text{CHCOCH}_3$		-78, 3 hr	$\text{CH}_2=\text{CH}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{COCH}_3$ (79)
3	(I)	$(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$		25, 5 min	$\text{CH}_2=\text{CHCH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{COCH}_3$ (87)
4	(III) ^e	$\text{PhCH}=\text{CHCOCH}_3$ ^f		-78, 0.5 min	$\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{CH}(\text{Ph})\text{CH}_2\text{COCH}_3$ (69)
5	(IV) ^g	$\text{PhCH}=\text{CHCOCH}_3$		-78, 5 hr	$\text{CH}_2=\text{CHCH}(\text{CH}_3)\text{CH}(\text{Ph})\text{CH}_2\text{COCH}_3$ (76)
6	(I)	$\text{PhCH}=\text{CHCOPh}$		-78, 1 min	$\text{CH}_2=\text{CHCH}_2\text{CH}(\text{Ph})\text{CH}_2\text{COPh}$ (96)
7	(I)			-78, 2 hr	 (70)
8	(III)			-78, 10 min	 (70)
9	(I)			-78, 2 hr	 (54)

TABLE 1 (contd.)

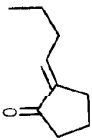
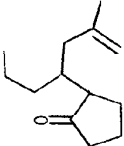
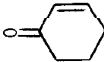
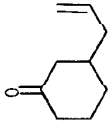
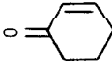
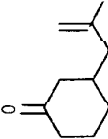
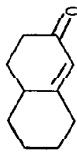
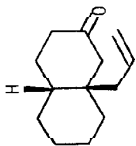
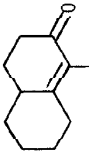
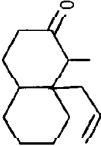
10	(III)		-78, 30 min		(82) ^h
11	(I)		-78, 1 hr		(80) ⁱ
12	(III)		-78, 10 min		(99)
13	(I) ^j		-78, 18 hr then -30, 5 hr		(85) ^k
14	(I)		-73, 2 hr then 0, 15 min		(88)

TABLE I (contd.)

^aThe reaction was carried out on a 1-20 mmol scale in dichloromethane. ^b Yields after isolation by distillation or thin layer chromatography. ^c(I): $\text{Me}_3\text{SiCH}_2\text{CH}=\text{CH}_2$. ^d(II): $\text{Me}_3\text{SiCH}_2\text{CH}=\text{C}(\text{CH}_3)_2$. ^e(III): $\text{Me}_3\text{SiCH}_2\text{C}(\text{CH}_3)\text{CH}_2$. ^fThree equivalents of the allylsilane were used. ^g(IV): $\text{trans-Me}_3\text{SiCH}_2\text{CH}=\text{CHCH}_3$. ^hA [2+2] cycloadduct assigned the structure 1-methyl-1-trimethylsilylmethyl-3-*n*-propylspiro[3.4]octan-5-one was obtained in 19% yield. ⁱB.p. 56-60°C (3 mm), n_D^{20} 1.4719. ^jTwo equivalents of the allylsilane were used. ^kB.p. 83-85°C (0.6 mm), n_D^{20} 1.5111. A diallylated product assigned the structure 2,8a-diallyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene was obtained as a forerun in less than 5% yield.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Phenyl-6-hepten-2-one: 6-Hepten-2-one, 4-phenyl- (10); (69492-29-1)

Benzalacetone: 3-Buten-2-one, 4-phenyl- (8,9); (122-57-6)

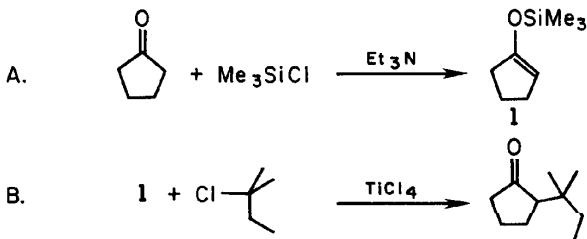
Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

Allyltrimethylsilane: Silane, allyltrimethyl- (8); Silane, trimethyl-2-propenyl- (9); (762-72-1)

α -tert-ALKYLATION OF KETONES:

2-tert-PENTYLCYCLOPENTANONE

(Cyclopentanone, 2-(tert-pentyl-))



Submitted by M. T. Reetz, I. Chatziiosifidis, F. Hubner, and H. Heimbach¹.

Checked by Kevin Kunnen and Carl R. Johnson.

1. Procedure

A. *1-Trimethylsilyloxycyclopentene*.² A 1-L, two-necked, round-bottomed flask is equipped with a mechanical stirrer and a reflux condenser having a drying tube (calcium chloride). The flask is charged with 200 mL of dimethylformamide (Note 1), 45 g (0.54 mol) of cyclopentanone (Note 2), 65.5 g (0.6 mol) of chlorotrimethylsilane (Note 2) and 185 mL (1.33 mol) of triethylamine (Note 1), and the mixture is refluxed for 17 hr (Note 3). The mixture is cooled, diluted with 350 mL of pentane, and washed four times with 200-mL portions of cold saturated aqueous sodium hydrogen carbonate. The

aqueous phases are extracted twice with 100-mL portions of pentane and the combined organic phases are washed *rapidly* with 100 mL of ice-cold aqueous 2 N HCl and immediately thereafter with a cold saturated solution of sodium hydrogen carbonate. After the mixture has been dried over anhydrous magnesium sulfate, the pentane is removed by rotary evaporation. Distillation of the oily residue at 60°C (12 mm) using a 20-cm Vigreux column affords 50.1-51.6 g (60-62%) of 1-trimethylsilyloxycyclopentene (1) as a colorless liquid (Note 4).

B. 3-tert-Pentylcyclopentanone. A dry, 250-mL, three-necked, round-bottomed flask is fitted with a gas inlet, a gas bubbler, rubber septum and magnetic stirrer. The apparatus is flushed with dry nitrogen or argon and charged with 120 mL of dry dichloromethane (Note 5), 15.6 g (0.10 mol) of 1-trimethylsilyloxycyclopentene and 11.7 g (0.11 mol) of 2-chloro-2-methylbutane (Note 6). The mixture is cooled to -50°C (Note 7) and a cold (-50°C) solution of 11 mL (0.10 mol) of titanium tetrachloride (Note 8) in 20 mL of dichloromethane is added within 2 min through the rubber septum with the aid of a syringe. During this operation rapid stirring and cooling is maintained. Sunlight should be avoided. The reddish-brown mixture is stirred at the given temperature for an additional 2.5 hr and is then rapidly poured into 1 L of ice water (Note 9). After the addition of 400 mL of dichloromethane, the mixture is vigorously shaken in a separatory funnel; the organic phase is separated and washed twice with 400-mL portions of water. The aqueous phase of the latter two washings is extracted with 200 mL of dichloromethane; the organic phases are combined and dried over anhydrous sodium sulfate. The mixture is concentrated using a rotary evaporator and the residue is distilled at 80°C (12 mm) (Note 10) to yield 9.2-9.5 g (60-62%) (Note 11) of 2-tert-pentylcyclopentanone as a colorless oil (Note 12).

2. Notes

1. Dimethylformamide and triethylamine were purchased from Baker (Baker Analyzed Reagent) and used without further purification.

2. Cyclopentanone and chlorotrimethylsilane were purchased from Aldrich Chemical Company and used without further purification.

3. According to the original procedure of House,² only four hours are needed, affording a 59% yield. However, the submitters found that an increase in reaction time raises the yield.

4. The spectral properties of the compound are as follows: ¹H NMR (CCl₄) δ: 0.2 (s, 9 H), 1.6-2.4 (m, 6 H), 4.4 (m, 1 H); IR (film) 1645 cm⁻¹ (lit.² 1645 cm⁻¹).

5. Reagent grade dichloromethane is dried by passing over a column of aluminum oxide (activity I).

6. The submitters purchased 2-chloro-2-methylbutane from Eastman Kodak Company. The checkers prepared the halide as follows. A separatory funnel was charged with 21.5 mL (0.2 mol) of 2-methyl-2-butanol and 100 mL of concd hydrochloric acid. The mixture was shaken vigorously with periodic venting for 10 min. The layers were separated and the 2-chloro-2-methylbutane layer (upper) was washed several times with equal volumes of cold water. The product was dried over calcium chloride and distilled, bp 85°C.

7. The precise temperature is not critical. The checkers observed that the reaction proceeds in about the same time and yield at -78°C. However, at temperatures above -40°C a drop in yield may occur.

8. The titanium tetrachloride should be clean, colorless, and free of hydrogen chloride. The checkers used material freshly distilled in an argon atmosphere.

9. If sodium bicarbonate is used, large amounts of titanium oxide-containing emulsions tend to form which hamper the purification of the product.

10. The by-products consist of volatile cyclopentanone and an unknown high boiling material, so that rapid vacuum transfer at room temperature and 0.02 mm is also possible. Extremely slow distillation at high temperatures should be avoided. The value of 72°C (2.2 mm) cited in the literature³ seems to be in slight error.

11. The submitters ran the reaction on a 0.5 scale and reported yields of 63-68%.

12. The product is > 96% pure as checked by gas chromatography (4% UCON LB 550X, Chromosorb G, AW-DMCS 80-100 mesh, 130°C). The spectral properties are as follows: IR (neat) cm^{-1} : 3050-2800, 1735, 1460, 1150; ^1H NMR (CCl_4) δ : 0.80 (J = 6 Hz, CH_3 of the ethyl group, which partially overlaps with the signals of the other two diastereotopic methyl groups), 0.82 (s), 0.92 (s), 1.15-2.25 (m); ^{13}C NMR (CDCl_3) δ : 7.78, 19.87, 23.72 (slightly broad), 25.57, 32.62, 34.70, 40.02, 55.39, 219.57.

3. Discussion

This procedure solves the long-pending problem of α -tert-alkylation of ketones. The generality is shown by the fact that a wide variety of structurally different ketones can be alkylated via the corresponding silyl enol ethers with good yields.⁴ Variation of the alkylating agent is also possible, branched and cyclic tertiary alkyl halides reacting position specifically without signs of rearrangement.⁴ Chemoselectivity studies reveal that esters, aromatic groups, and primary alkyl halide moieties are tolerated.⁴ In the

case of a sensitive enol ether such as that derived from acetone, titanium tetrachloride should be replaced by more mild Lewis acids such as zinc chloride, although the yields are lower.⁵ Finally, it should be noted that any S_N1 -reactive alkyl halide is likely to be a suitable alkylating agent in Lewis acid promoted α -alkylation of carbonyl compounds. Indeed, aryl-activated secondary alkyl halides react in the same way.⁶ Generally, such alkylating agents are unsuitable in classical enolate chemistry because of the ease of hydrogen halide elimination and/or the failure to react regiospecifically. The methods are thus complementary.

A related tert-butylation procedure in which the silyl enol ether is added to a mixture of titanium tetrachloride and tert-butyl chloride gives rise to distinctly lower yields.^{7,8} This is also the case if the tertiary halide is added to a mixture of silyl enol ether and titanium tetrachloride.⁵

A number of alternative multi-step procedures for the synthesis of α -tert-alkyl ketones are known, none of which possess wide generality. A previous synthesis of 2-tert-pentylcyclopentanone involved reaction of N-1-cyclopentenylpyrrolidine with 3-chloro-3-methyl-1-butyne and reduction of the resulting acetylene (overall yield 46%).³ However, all other enamines tested afford much lower yields.³ Cuprate addition to unsaturated ketones may be useful in certain cases.⁹ Other indirect methods have been briefly reviewed.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2-tert-Pentylcyclopentanone: Cyclopentanone, 2-tert-pentyl (8,9);
(25184-25-2)

Cyclopentanone (8,9); (120-92-3)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (15-11-4)

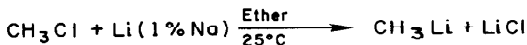
1-Trimethylsilyloxycyclopentene: Silane, (1-cyclopenten-1-yloxy)trimethyl-
(8,9); (19980-43-9)

2-Chloro-2-methylbutane: Butane, 2-chloro-2-methyl- (8,9); (594-36-5)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

PREPARATION OF HALIDE-FREE METHYLLITHIUM

(Lithium, methyl-)



Submitted by Michael J. Lusch, William V. Phillips, Ronald F. Sietloff,

Glenn S. Nomura, and Herbert O. House¹.

Checked by Gregory S. Bisacchi and Robert V. Stevens.

1. Procedure

Caution! The fine lithium dispersion used in this preparation, once washed to remove the mineral oil coating, will ignite spontaneously if exposed to air. Also, the methyl chloride and ether used are very volatile and highly flammable. The entire preparation including the disposal of any residual lithium should be performed in an efficient hood with a safety shield in front of the apparatus. A suitable dry-powder fire extinguisher should be kept at hand to extinguish any fires resulting from the accidental spillage of the washed lithium dispersion or of the methyllithium solution.

A dry 1-L, three-necked, round-bottomed flask equipped with a large Teflon-covered magnetic stirring bar, a thermometer, and a dry ice condenser (Note 1) is flushed with argon (Note 2), then capped with a serum stopper and subsequently maintained under a positive pressure of argon (Note 3). A 30% dispersion of lithium metal (in mineral oil) containing 1% sodium (13.9 g, 2.00 g-atom of lithium) (Note 4) is rapidly weighed and transferred to the flask.

The lithium is washed three times by transferring approximately 150-mL portions of anhydrous ethyl ether (Note 5) into the flask through the serum stopper by forced siphon through a stainless steel cannula, stirring the resulting suspension of lithium briefly, allowing the lithium to rise to the surface, and finally withdrawing the major part of the underlying ether by forced siphon through a cannula. Anhydrous ethyl ether (500 mL) is added to the resultant oil-free lithium. Methyl chloride gas (bp -24°C , $d_{-24^{\circ}\text{C}}$ 0.99 g/mL) from a compressed gas cylinder is passed through a flask containing 4Å molecular sieves and into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry ice condenser, and cooled to -24°C with a bath of dry ice-acetone (Fig. 1). When 52.7 mL (52.5 g, 1.04 mol) of liquid methyl chloride has been collected, the adapter and condenser are removed, several boiling chips are added to the cold (-24°C) graduated cylinder, and the cylinder is stoppered with a rubber septum through which is inserted a stainless steel cannula. The other end of this cannula is inserted through the rubber septum of the flask so that its tip is just above the liquid surface of the reaction flask. Dry ice-acetone is then added to the condenser attached to the reaction flask. Vigorous stirring of the ethereal lithium dispersion is begun and the methyl chloride is added over approximately a 1.5-hr period. The rate at which methyl chloride is distilled into the reaction vessel is controlled by slight cooling or warming of the graduated cylinder which contains the liquid methyl chloride. During addition, the initial grey suspension changes to a brown to purple suspension; by the end of the addition, little if any lithium metal should be seen floating on the surface of the ether solution when stirring is interrupted. After the addition of methyl chloride is complete, the reaction mixture is stirred at 25°C for an additional 0.5-1 hr and then allowed to stand overnight

or longer (Note 6) at 25°C under a static argon atmosphere, whereupon the precipitated lithium chloride settles to the bottom of the flask. The dry ice condenser and thermometer are removed from the flask and replaced with rubber septa. The supernatant methyllithium solution is transferred by forced siphon using a large-gauge cannula through a glass wool pad (Note 7) into a receiving flask previously flushed with an inert gas (Fig. 2). The receiving flask which contains the filtrate, a pale yellow solution of methyllithium, is removed (Note 8) and stored in a refrigerator for 12-24 hr during which time an additional small quantity of lithium chloride separates as fine crystals. The resulting supernatant solution is transferred with a stainless steel cannula and a slight positive pressure of argon or nitrogen into one or more suitable oven-dried nitrogen-filled storage bottles capped with rubber septa. Two 1-mL aliquots of the solution are removed with a hypodermic syringe for a modified Gilman titration (Note 9) and a 5-mL aliquot is removed with a hypodermic syringe to determine the halide concentration (Note 10). The solution contains 1.40-1.77 M methyllithium accompanied by 0.07-0.09 M lithium chloride corresponding to a 70-89% yield of methyllithium. If this solution is protected from oxygen and moisture, it may be stored at 0-25°C for several months (and remain active).

2. Notes

1. The dry ice condenser used with the apparatus should have sufficient condensing capacity to prevent the loss of significant amounts of methyl chloride; a condenser 38 cm long and 3.8 cm in diameter was suitable.

2. Since finely divided lithium floats on the surface of the solvent and will be in contact with the atmosphere in the reaction vessel, an argon atmosphere, rather than a nitrogen atmosphere, should be used to avoid formation of the insoluble reddish-brown lithium nitride.

3. A slight positive pressure of argon was maintained in the vessel throughout the reaction by using an argon line connected to both a bubbler containing Nujol and the inlet on the dry ice condenser.

4. A dispersion in mineral oil of 30% (by weight) of lithium containing 1% by weight of sodium is marketed by Alfa Products, Morton/Thiokol, Inc. This oil-coated dispersion may be exposed to the air during transfer and weighing and is conveniently transferred from its container by pouring through a wide-mouth funnel. Small quantities of the dispersion which adhere to the apparatus may be disposed of by rinsing in a stream of warm water to lower the viscosity of the oil and allow the suspended lithium to react with water at a controlled rate. To dispose of large quantities of this dispersion (or any quantity of lithium powder no longer coated with oil), the material should be suspended in anhydrous ether under an argon atmosphere and t-butyl alcohol should be added dropwise to the suspension until all of the lithium metal has been consumed. Since hydrogen is liberated during these disposal procedures, they should be performed in an efficient hood.

5. Anhydrous ethyl ether was distilled from lithium aluminum hydride immediately before use.

6. Although most of the lithium chloride separates from the ether solution as a finely divided solid during the reaction, additional small quantities of lithium chloride continue to separate for 12-14 hr. After standing overnight, a typical reaction contains a precipitate of finely divided brownish-pink solid below a clear, pale yellow solution.

7. A convenient filter was constructed by packing glass wool, previously dried in an oven, into a 20-mL Luer-lok syringe barrel fitted with a 15 gauge needle. The syringe barrel was capped with a serum stopper. A large diameter cannula (at least 15 gauge) should be used to transfer the methyllithium solution from the flask to the filter since smaller gauge cannulae are frequently plugged by solid particles.

8. As soon as the receiver containing the methyllithium solution has been removed and stoppered, the residual solids in the reaction flask and the filtration apparatus should be rinsed into another receiver with anhydrous ether under an atmosphere of argon or nitrogen. The ether slurry of solids, which may contain some unchanged lithium metal, should be treated cautiously in a hood with *t*-butyl alcohol to consume any residual lithium metal before the mixture is discarded.

9. One 1-mL aliquot is added to 1.0 mL of freshly-distilled 1,2-dibromoethane (bp 132°C) in an oven-dried flask which contains a static atmosphere of nitrogen or argon. After the resulting solution has been allowed to stand at 25°C for 5 min, it is diluted with 10 mL of water and titrated for base content (residual base) to a phenolphthalein endpoint with standard 0.100 M hydrochloric acid. The second 1-mL aliquot is added cautiously to 10 mL of water and then titrated for base content (total base) to a phenolphthalein endpoint with standard aqueous 0.100 M hydrochloric acid. The methyllithium concentration is the difference between the total base and residual base concentrations.² Alternatively, the methyllithium concentration may be determined by titration with a standard solution of *sec*-butyl alcohol employing 2,2'-bipyridyl as an indicator.^{3a,b}

10. To determine the concentration of chloride ion,^{3c,d} a 5-mL aliquot of the methyllithium solution is cautiously added to 25 mL of water and the resulting solution is acidified with concentrated sulfuric acid and then treated with 2-3 mL of ferric ammonium sulfate $[\text{Fe}(\text{NH}_4)(\text{SO}_4)_2 \cdot 12 \cdot \text{H}_2\text{O}]$ indicator solution and 2-3 mL of benzyl alcohol. The resulting mixture is treated with 10.0 mL of standard aqueous 0.100 M silver nitrate solution and then titrated with standard aqueous 0.100 M potassium thiocyanate solution to a brownish-red endpoint.

3. Discussion

Although ethereal solutions of methyllithium may be prepared by the reaction of lithium wire with either methyl iodide⁴ or methyl bromide⁵ in ether solution, the molar equivalent of lithium iodide or lithium bromide formed in these reactions remains in solution and forms, in part, a complex with the methyllithium.⁶ Certain of the ethereal solutions of methyllithium currently marketed by several suppliers including Alfa Products, Morton/Thiokol, Inc., Aldrich Chemical Company, and Lithium Corporation of America, Inc., have been prepared from methyl bromide and contain a full molar equivalent of lithium bromide. In several applications such as the use of methyllithium to prepare lithium dimethylcuprate⁷ or the use of methyllithium in 1,2-dimethoxyethane to prepare lithium enolates from enol acetates or trimethylsilyl enol ethers,^{3b} the presence of this lithium salt interferes with the titration and use of methyllithium. There is also evidence which indicates that the stereochemistry observed during addition of methyllithium to carbonyl compounds may be influenced significantly by the presence of a lithium salt in the reaction solution.⁸ For these reasons it is often desirable to have ethereal solutions

of methyllithium that do not contain an equivalent amount of lithium iodide or lithium bromide.

The reaction of lithium with methyl chloride in ether solution produces a solution of methyllithium from which most of the relatively insoluble lithium chloride precipitates. Ethereal solutions of "halide-free" methyllithium, containing 2-5 mole percent of lithium chloride, were formerly marketed by Foote Mineral Company and by Lithium Corporation of America, Inc., but this product has been discontinued by both companies. Comparable solutions are also marketed by Alfa Products and by Aldrich Chemical Company; these solutions have a limited shelf-life and older solutions have often deteriorated badly even before the container is opened. Since an ether solution of methyl chloride reacts very slowly with lithium wire used in reactions with methyl bromide or methyl iodide, the present procedure⁹ uses a finely divided suspension of lithium metal containing 1% (by weight) of sodium^{6,10} to achieve a rapid reaction with methyl chloride. The finely divided lithium containing 1% sodium is marketed as a 30% (by weight) dispersion in mineral oil and must be washed free of this protective hydrocarbon diluent before use in order to avoid contamination of the final methyllithium reagent with a substantial amount of a mixture of high molecular weight hydrocarbons. Since lithium is less dense than common organic solvents such as diethyl ether or pentane, the washing procedure must be done with special care to avoid starting a fire with the pyrophoric, finely-divided lithium.^{2b} Finely divided lithium with somewhat higher or lower percentages of sodium are expected to work equally well.

1. School of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl chloride: Methane, chloro- (8,9); (74-87-3)

Lithium (8,9); (7439-93-2)

Methyl lithium: lithium, methyl- (8,9); (917-54-4)

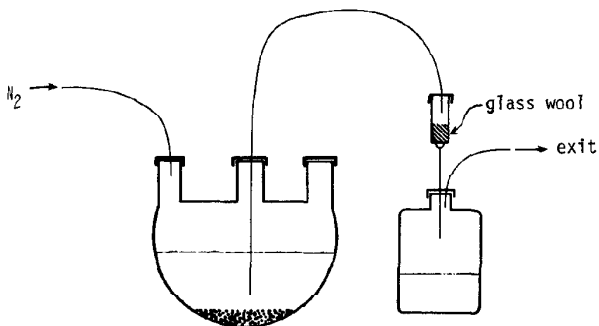


Figure 2. Decanting the methyl lithium solution

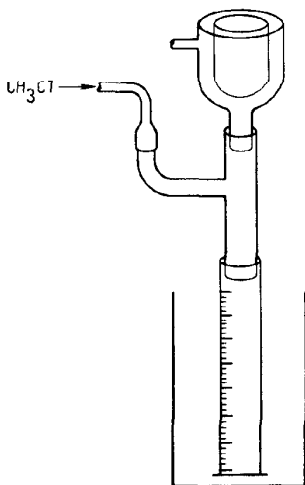
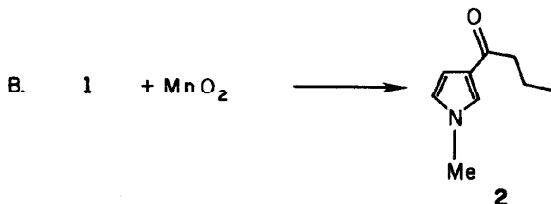
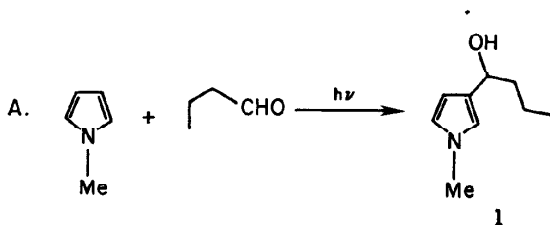


Figure 1. Condensing the methyl chloride

3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE AND 3-BUTYROYL-1-METHYLPYRROLE

(1H-Pyrrole-3-methanol, 1-methyl- α -propyl- and 1-Butanone,

1-(1-methyl-1H-pyrrol-3-yl)-)



Submitted by H. M. Gilow and G. Jones, II¹.

Checked by Steven M. Pitzenberger, Richard A. Hayes, and Orville L. Chapman.

1. Procedure

A. *3-(1-Hydroxybutyl)-1-methylpyrrole* (1). A photochemical quartz immersion well (220 mm length) (Note 1) equipped with 450-watt Hanovia medium pressure mercury lamp and a Vycor filter, cooled with water, is used. To a 125-mL Pyrex reaction vessel (230 mm long, 64 mm i.d.) equipped with a gas inlet and outlet, is added 60 mL (55 g, 0.676 mol) of 1-methylpyrrole (Note 2)

and 65 mL (54 g, 0.936 mol) of butyraldehyde (Note 3). Dry nitrogen is slowly bubbled through the solution during 48 hr of photolysis (Note 4).

The solution is concentrated under reduced pressure. The remaining oil is distilled under reduced pressure using a simple distillation apparatus. After a small forerun, 27 g (0.179 mol, 26% yield) (Note 5) of 1 is collected, as a light yellow oil, bp 90-94°C/0.05 mm (Note 6). Further purification is accomplished by a second distillation under reduced pressure, bp 90.2°C/0.05 mm (Notes 7 and 8).

B. *3-Butyroyl-1-methylpyrrole* (2). A 100-mL, one-necked, round-bottomed flask is fitted with an efficient reflux condenser and arranged for magnetic stirring and heating. The flask is charged with 50 mL of pentane (Note 9) and 2.0 g (13 mmol) of 1 (Note 10). To the rapidly-stirred solution is added 16 g (180 mmol) of activated manganese(IV) oxide (Note 11) in small portions over 5 min. The solution is heated at reflux for 18 hr and then an additional 8 g (90 mmol) of activated manganese(IV) oxide is added in portions (Note 12). After being heated at reflux for 24 hr, the reaction mixture is filtered through a 2-cm Celite filter pad. The filtered manganese oxides are thoroughly washed with about 200-300 mL of dichloromethane. Evaporation of solvent from the combined filtrates leaves 1.4-1.6 g of a light yellow oil. Bulb-to-bulb distillation at 100°C/0.1 mm (Note 13) gives 1.27-1.40 g (8.4-9.3 mmol, 64-71% yield) of an oil (2) (Note 14).

2. Notes

1. The photochemical quartz immersion well was obtained from Ace Glass Inc.

2. 1-Methylpyrrole was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 112-112.5°C.

3. Butyraldehyde was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 74.5-75.5°C. It is important that a freshly distilled sample, free of trimer, be used, or the final product will be contaminated with trimer.

4. When the reaction mixture was monitored by GLC (500-mm x 3.2-mm column, packed with 5% OV 101 on chromosorb G, HP, 100/120 mesh) most of the product was formed in the first 24 hr of photolysis, as shown by the following profile:

<u>Time of Photolysis</u>	<u>% of Alcohol (Based on Starting Pyrrole)</u>
2 hr	4
19 hr	18
24 hr	23
48 hr	25

5. The checkers found that the distillate contained 15-30% butyraldehyde (as monitored by NMR), which depended upon the efficiency of the distillation. A 10-cm column packed with glass helices was the most efficient, but the yield of distilled product dropped drastically.

6. The susceptibility of 3-(1-hydroxybutyl)-1-methylpyrrole to air oxidation and decomposition with acid requires that prolonged storage be done in tightly capped containers in a refrigerator.

7. The spectral properties of 3-(1-hydroxybutyl)-1-methylpyrrole are as follows: ^1H NMR (CDCl_3) δ : 0.90 (t, 3 H, $\text{CH}_3\text{-C}$), 1.10-1.80 (m, 4 H, $-\text{CH}_2\text{CH}_2-$), 2.88 (s, 1 H, H-O-), 3.51 (s, 3 H, $\text{CH}_3\text{N-}$), 4.50 (t, 1 H, HC-), 5.9 (t, 1 H, 4-pyrrole) and 6.41 (d, 2 H, 2,5-pyrrole). IR (neat) cm^{-1} : 3400 (H-O stretch) and 1175 (C=O stretch).

8. The reaction can also be carried out using smaller amounts of 1-methylpyrrole (0.113 mol), butyraldehyde (0.113 mol) and a solvent (245 mL acetonitrile, ACS grade) in a somewhat larger reaction vessel. After 17 hr of photolysis, and after removal of the volatile material and distillation of the remaining oil under reduced pressure, 4-5 g of the alcohol is isolated.

9. The submitters used dichloromethane. The checkers found that use of pentane² resulted in increased yields for the oxidation.

10. When the alcohol (1) is contaminated with small amounts of butyraldehyde, oxidation proceeds with a much lower yield of product.

11. Activated manganese(IV) oxide was purchased from Alfa Products, Morton/Thiokol, Inc.

12. Progress of the reaction can be monitored by taking an aliquot of the reaction, filtering it, removing the solvent in a vacuum, dissolving the residual oil in carbon tetrachloride, and observing the ^1H NMR spectrum. Relative integration of the proton resonances of the pyrrole 2-position (6.1 ppm for the alcohol and 7.2 ppm for the ketone) gives an indication of the percent conversion. The checkers found only 77% conversion after the first reflux period. A higher conversion, 90-97%, was achieved after a second addition of activated manganese(IV) oxide and subsequent heating at reflux.

13. The submitters used a short path simple distillation apparatus; bp $85-87^\circ\text{C}$ (0.2 mm).

14. The following spectral properties were recorded for 3-butyroyl-1-methylpyrrole, 2: ^1H NMR (CDCl_3 , 200 MHz) δ : 0.97 (t, 3 H), 1.72 (sextet, 2 H), 2.68 (t, 2 H), 3.68 (s, 3 H), 6.6 (m, 2 H, 4,5-pyrrole), 7.23 (t, 1 H, 2-pyrrole); IR (neat) cm^{-1} : 1660 (C=O stretch); MS (70 eV) m/e (rel. int.): 151 (8.6, M^+), 123 (1.6), 108 (34), 28 (100). The submitters reported the following spectral data: ^1H NMR (CDCl_3) δ : 0.95 (t, 3 H), 1.65 (sextet, 2 H), 2.65 (t, 2 H), 3.63 (s, 3 H), 6.47 (m, 2 H), 7.15 (m, 1 H); IR (neat) cm^{-1} : 1700.

3. Discussion

This procedure provides a method for functionalizing the pyrrole ring in the 3-position, normally a difficult synthetic step when conventional electrophilic substitution is used.³ The technique has been extended to addition of several aldehydes and acetone and to a number of pyrroles.⁴ The generality includes photoaddition to imidazoles which are substituted in the 4-position. Pyrrole photoadduct alcohols are readily dehydrated to 3-alkenylpyrroles or oxidized to 3-acyl derivatives.

The precedent is strong for the involvement of oxetanes as intermediates in carbonyl additions to pyrroles.⁵⁻⁷ NMR evidence has been obtained for an oxetane adduct of acetone and N-methylpyrrole.⁴ The initial photoadduct was shown to rearrange readily on workup to the 3-(hydroxyalkyl)pyrrole derivative.

Oxidation of the 3-(hydroxyalkyl)pyrrole derivative gives a pure 3-acylpyrrole derivative which is difficult to obtain by direct substitution in the pyrrole ring. Acylation of pyrrole yields 1- and/or 2-acetylpyrrole, whereas acylation of 1-methylpyrrole forms both 2- and 3-acetyl-1-methyl-

pyrrole, the latter in smaller amount.³ When a similar procedure was used, 3-(1-hydroxyethyl)-1-methylpyrrole was converted to 3-acetyl-1-methylpyrrole in 76% yield.⁴ Recently the decarbonylation of 1-methyl-4-acetyl-2-pyrrol-aldehyde was used as a method to prepare 3-acetyl-1-methylpyrrole.⁸

1. Department of Chemistry, Boston University, Boston, MA 02215 (H. M. G. on leave from Southwestern at Memphis, Memphis, TN 38112). This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-(1-Hydroxybutyl)-1-methylpyrrole: 1 H-Pyrrole-3-methanol, 1-methyl- α -propyl- (10); 70702-66-8

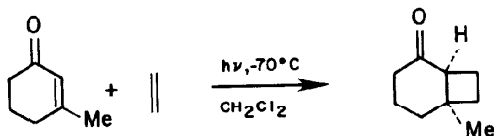
3-Butyroyl-1-methylpyrrole: 1-Butanone, 1-(1-methyl-1 H-pyrrol-3-yl)- (10); 62128-46-5

1-Methylpyrrole: Pyrrole, 1-methyl- (8); 1 H-Pyrrole, 1-methyl- (9); 96-54-8
Butyraldehyde (8); Butanal (9); 123-72-8

PHOTOCYCLIZATION OF AN ENONE TO AN ALKENE:

6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE

(Bicyclo[4.2.0]octan-2-one, 6-methyl-)



Submitted by R. L. Cargill,^{1a} J. R. Dalton, G. H. Morton, and W. E. Caldwell¹.

Checked by Barry A. Wexler, Amos B. Smith, III, and Carl R. Johnson.

1. Procedure

The irradiation apparatus (Note 1) is charged with a solution of 25.0 g (0.277 mol) of 3-methyl-2-cyclohexenone (Note 2) in reagent grade dichloromethane (Note 3). A gas outlet tube to an efficient hood is placed in one 14/20 standard taper joint; in the other, there is a stopper which can be removed for periodic sampling. The cooling water is turned on (Note 4) and the apparatus is immersed in a dry ice/2-propanol bath while the chilled solution is saturated with ethylene (Note 5). The lamp is inserted into the well and turned on (Note 6). Progress of the irradiation is conveniently followed by gas chromatography (Note 7). After ca. 8 hr, most of the starting material has reacted. At this time, the lamp is turned off and the apparatus removed from the cooling bath. The reaction mixture is degassed with a slow stream of nitrogen while it warms to room temperature, dried over magnesium

sulfate, and concentrated with a rotary evaporator at a temperature below 30°C (Note 8). The product is isolated by distillation to afford 27-28 g (86-90%) of 6-methylbicyclo[4.2.0]octan-2-one, bp 62-65°C (3.5 mm) (Notes 9 and 10).

2. Notes

1. The apparatus is similar to one described earlier.² A triple-walled Dewar is constructed of Pyrex according to Figure 1. For further discussion concerning this immersion well contact Joel M. Babbitt, Glassblower, Department of Chemistry, University of South Carolina, Columbia, SC 29208. The evacuated jacket permits the safe use of circulating tap water as a lamp coolant even when irradiations are conducted in a dry-ice bath. A further advantage is that three layers of Pyrex constitute an effective filter for light in the 280-300 nm region so that secondary photolysis of cycloadducts is not usually observed. The irradiation flask is a cylindrical vessel of suitable volume fitted with a coarse, fritted disc for gas dispersion and a flanged lip. The light source is either a G.E. H1000-A36-15, Westinghouse H-36GV-1000, or equivalent lamp with the outer globe removed, used in conjunction with a G.E 35-9627-6009 ballast. These lamps are available from the General Electric Company, Lamp Division, Charlotte, North Carolina.

2. This material can be purchased from Aldrich Chemical Co. or it can be prepared from Hagemann's ester.³

3. The volume of solution will vary depending on the exact volume of the apparatus, the temperature, and the miscibility of gaseous reactant in the solvent. The solution should completely surround the lamp, but should not overflow the vessel. The submitters used a volume of 1100 mL and the checkers used 200 mL.

4. If the flow of cooling water is stopped while the apparatus is cold, the water may freeze and crack the immersion well. The vacuum jacket provides greater insurance against this problem than is available in the commercially available wells used with the usual 450 watt lamps.²

5. CP grade ethylene (Matheson) was used without purification. A flow of ca. 100 mL/min of ethylene for 2-3 hr is adequate for saturation. Gas flow is continued throughout the irradiation in order to maintain a high concentration of ethylene and for stirring.

6. The lamp will not start if it is too cold or too hot. The practice of blowing nitrogen over the lamp to remove ozone is not recommended as this cools the lamp and decreases its output significantly, resulting in an unnecessarily long irradiation period.

7. The submitters used a Varian 1200 FID chromatograph with a 7% Carbowax 20 M on Chromosorb Q, 8-ft x 0.125-in column, a carrier gas (N_2) flow rate of 40 mL/min, column 160°C, injector 220°C, detector 215°C. Retention times were 3-methyl-2-cyclohexanone, 4.2 min, and 6-methylbicyclo[4.2.0]octan-2-one, 3.9 min, respectively.

8. If the solvent is removed without care a considerable amount of volatile product may be lost.

9. This material is contaminated with ~10% of 3-methylcyclohexenone. Material of greater purity can be obtained by extending the time of irradiation, by carrying out an efficient distillation of product, or by decomposing starting material with potassium permanganate prior to distillation.

10. The product has the following spectral properties: IR (CCl_4) cm^{-1} : 1700; 1H NMR (CCl_4) δ : 1.21 (s, 3 H, methyl), 1.9 (m, 11 H, all other protons); ^{13}C NMR (C_6D_6) δ (based on δ C_6D_6 128.00): 211.63, 51.34, 40.86, 39.45, 35.26, 31.20, 28.84, 21.45, 20.35; ms (m/e) 138.1041 (parent ion).

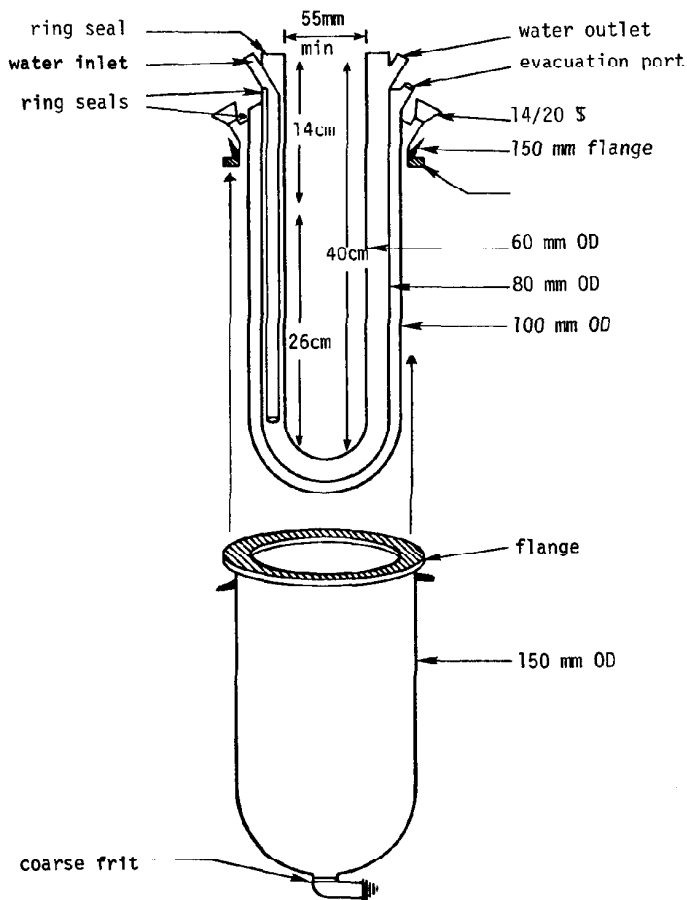


Figure. Irradiation Vessel

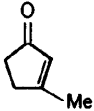
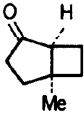
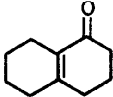
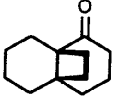
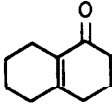
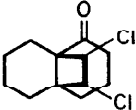
3. Discussion

Although photochemical cycloadditions have gained acceptance in synthetic chemistry,⁴ most such reactions are limited to a relatively small scale. The use of a 1000-watt street lamp permits the irradiation of up to 1 mol of substrate in less time than 0.2 mol can be irradiated with the conventional 450-watt lamps. Thus, under optimum conditions, the submitters were able to add ethylene to 3-methylcyclohexenone on a 20-g scale in 48 hr (80%) with a 450-watt lamp; with the apparatus described here 94 g of this enone was condensed with ethylene in 8 hr (91%).

Some general points regarding photochemical cycloadditions deserve mention. (1) Since the reaction is first order in olefin, the concentration of olefin (especially gaseous olefins) is of critical importance; therefore, the cycloadditions are carried out at low temperature. In some cases, however, low temperature can be detrimental.⁵ (2) Since lamp output deteriorates with lamp age, the rates of otherwise identical cycloadditions are unlikely to be the same; therefore, it is of critical importance that the progress of each photochemical reaction be followed by some suitable means (GLC, IR, UV, NMR, etc). (3) As long as all the incident light of appropriate wavelength is absorbed by the enone the reaction proceeds at a rate independent of enone concentration; thus, the highest concentration of enone at which dimerization can be avoided is optimal.

Several examples of preparative cycloadditions are listed in Table I.

TABLE I
PREPARATIVE-SCALE CYCLOADDITIONS

Entry	Enone	Weight (g)	Olefin	Time (hr)	Product(s)	Yield (%)
1.		25	C_2H_4	12		90 (ref 6)
2.		10	C_2H_4	6		71 (ref 7)
3.		20	$ClHC=CHCl$	10		93 ^a (ref 8)

^aA mixture of *cis* and *trans* olefins was used; a mixture of diastereomeric products was obtained. Both olefins give similar mixtures.

1. Department of Chemistry, University of South Carolina, Columbia, SC 29208. a) Present address: Cargill Interests, Ltd., P.O. Box 992, Longview, TX 75606.
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Appendix

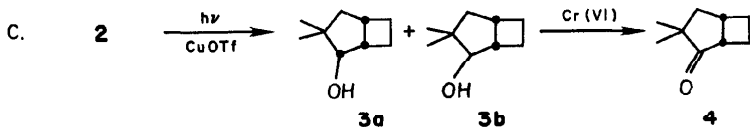
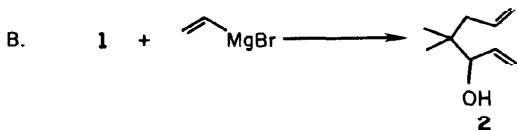
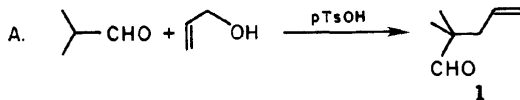
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6-Methylbicyclo[4.2.0]octan-2-one: Bicyclo[4.2.0]octan-2-one, 6-methyl- (8,9); (13404-66-5)

3-Methyl-2-cyclohexenone: 2-Cyclohexen-1-one, 3-methyl- (8,9); (1193-18-6)

Ethylene (8); Ethene (9); (74-85-1)

COPPER (I)-CATALYZED PHOTOCYCLOADDITION:
3,3-DIMETHYL-*cis*-BICYCLO[3.2.0]HEPTAN-2-ONE
(Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl-)



Submitted by Robert G. Salomon and Subrata Ghosh¹.

Checked by Daniel K. Jackson and Richard E. Benson.

1. Procedure

A. *2,2-Dimethyl-4-pentenal*. In a 500-mL, one-necked, round-bottomed flask which contains a magnetic stirring bar are placed 108 g (1.5 mol) of isobutyraldehyde (Note 1), 58 g (1.0 mol) of allyl alcohol (Note 1), 230 mL of p-cymene (Note 1), and 0.4 g (2 mmol) of p-toluenesulfonic acid monohydrate

(Note 1). The mixture is heated with a mantle with stirring for 32 hr under a 50-cm fractionating column packed with 6-mm glass beads and topped by a Dean-Stark trap. The reaction mixture is then distilled through the packed column. The fraction which boils at 120°-126°C is collected. The yield is 86.0-87.3 g (77-78%) of 2,2-dimethyl-4-pentenal (1) as a clear, colorless oil, n_D^{25} 1.4216 (Note 2).

B. *4,4-Dimethyl-1,6-heptadien-3-ol*. In a 1-L, three-necked, round-bottomed flask, fitted with mechanical stirrer, 500-mL pressure-equalizing addition funnel, and condenser topped with a gas inlet for maintaining an atmosphere of dry nitrogen, is placed 17 g (0.7 g-atom) of magnesium turnings (Note 3). The system is flushed with nitrogen, and methanol maintained at -20°C is circulated through the condenser (Note 4). From a solution of 70 g (0.65 mol) of vinyl bromide (Note 5) in 400 mL of tetrahydrofuran (Note 6), a 50-mL quantity is added by means of the addition funnel, and the resulting mixture is stirred mechanically. After a few minutes an exothermic reaction ensues which subsides after several minutes of vigorous boiling (Note 7). The remainder of the vinyl bromide solution is added at such a rate as to maintain a gentle reflux. After stirring at room temperature for 12 hr, the resulting mixture is cooled with an ice-water bath, and 62 g (0.55 mol) of 2,2-dimethyl-4-pentenal (1) is added dropwise over 25-30 min through the addition funnel which is then rinsed with 10 mL of dry tetrahydrofuran. The resulting mixture is stirred for 1 hr at 23°C and then poured into a mixture of 1 kg of ice, 200 mL of concd hydrochloric acid, and 400 mL of water. The resulting mixture is extracted with three 500-mL portions of ether. The combined extracts are washed successively with 400 mL of water, 400 mL of saturated aqueous sodium bicarbonate, and 400 mL of saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. The drying agent is removed by filtration and

the ether is removed with a rotary evaporator. Distillation of the product through a 15-cm vacuum-jacketed Vigreux column gives 63.4-63.8 g (82-83% yield) of 4,4-dimethyl-1,6-heptadien-3-ol (2), bp 76-79°C (20 mm), n_D^{24} 1.4562 (Note 8).

C. 3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-ol. A 25-mL test tube is charged with 0.3-0.4 g (0.6-0.8 mmol) of bis(copper trifluoromethanesulfonate)benzene complex (Note 9) and sealed with a rubber septum under an atmosphere of dry nitrogen. A solution of 5 mL (4.3 g, 0.031 mol) of 4,4-dimethyl-1,6-heptadien-3-ol in 10 mL of ether (Note 10) is added by means of a syringe. The resulting solution is poured (Note 11) into a nitrogen-flushed Pyrex 250-mL annular reactor fitted with a magnetic stirrer, an internal concentric water-jacketed quartz immersion well, and a water-cooled reflux condenser topped with a gas inlet for maintaining an atmosphere of dry nitrogen. An additional 20 mL (17.4 g, 0.124 mol) of the hydroxydiene 2 in 200 mL of dry ether is added. The resulting solution is stirred and irradiated for 15 hr with a 450-watt medium pressure Hanovia mercury arc (Note 12) which is suspended in the immersion well. At the end of that time an opaque film of copper is wiped from the immersion well, and irradiation is then continued for an additional 7 hr. The resulting solution is shaken in a separatory funnel with a mixture of 100 g of ice and 100 mL of concd aqueous ammonium hydroxide. The organic phase is separated and the aqueous phase is extracted with 100 mL of ether. The organic phases are combined and washed with 100 mL of saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 19.0-19.9 g (88-92% yield) of 3,3-dimethyl-cis-bicyclo[3.2.0]heptan-2-ol (3), bp 80-84°C (12 mm), n_D^{25} 1.4761-1.4783 (Note 13).

D. *3,3-Dimethyl-cis-bicyclo[3.2.0]heptan-2-one*. In a 500-mL Erlenmeyer flask which contains a magnetic stirring bar is placed 35.1 g (0.25 mol) of 3,3-dimethyl-cis-2-bicyclo[3.2.0]heptanol and 200 mL of acetone (Note 14). The solution is cooled with an ice-water bath while 100 mL of 2.7 M Jones reagent (Note 15) is added in small portions over 15 min with vigorous stirring (Note 16). The ice-water bath is removed and the reaction mixture is stirred at 5-20°C for 2 hr. Then 400 mL of saturated aqueous sodium chloride is added, and the resulting mixture is extracted with three 500-mL portions of ether. The extractions are combined and washed successively with 400 mL of saturated aqueous sodium chloride and 200 mL of saturated aqueous sodium bicarbonate. The solvent is removed by means of a rotary evaporator and the resulting product is transferred to a separatory funnel and separated from the water. The aqueous layer is extracted with 50 mL of ether. The product and the ether layer are combined and dried over anhydrous sodium sulfate. The ether is removed by distillation using a rotary evaporator and the product is distilled through a 15-cm vacuum-jacketed Vigreux column to give 28.7-32.2 g (83-93% yield) of 3,3-dimethyl-cis-bicyclo[3.2.0]heptan-2-one (4), bp 72-75°C (12 mm), n_D^{20} 1.4622 (Note 17).

2. Notes

1. Isobutyraldehyde, allyl alcohol, p-cymene, and p-toluenesulfonic acid monohydrate were purchased from Aldrich Chemical Company, Inc., and used as received.

2. The submitters state that the distilled product was about 97% pure as shown by GLC analysis on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh and operated at 140°C. The retention time is about

1.40 min. Two minor impurities with retention times of about 0.95 and 1.15 min were detected, in roughly equal amounts. The product has the following spectral properties: IR (neat) cm^{-1} : 2965 (m), 2925 (m), 1725 (vs), 1465 (m), and 915 (m), together with numerous weaker absorption bands; ^1H NMR (CDCl_3) δ : 1.04 (s, 6 H), 2.22 (d, 2 H, $J = 7.0$), 4.9-5.3 (m, 2 H), 5.4-6.2 (m, 1 H), 9.40 (s, 1 H).

3. Reagent available from Fisher Scientific Company was used.

4. A Neslab ULT-80 refrigerated circulating bath was used. Alternatively, a Dewar condenser cooled with acetone-dry ice can be used.

5. Vinyl bromide, available from Aldrich Chemical Company Inc., was used as received.

6. Tetrahydrofuran, anhydrous, 99.9% (water content <0.006%) was purchased from Aldrich Chemical Company, Inc., and used as received. The vinyl bromide solution was prepared in a 500-mL, round-bottomed flask fitted with a glass stopper. The stoppered flask containing the tetrahydrofuran was chilled to about 5°C and weighed. The vinyl bromide, also chilled to about 5°C , was rapidly poured into the tetrahydrofuran until the desired amount had been added. The flask was stoppered, the contents mixed by shaking, allowed to warm to about 16°C , and then added to the pressure-equalizing addition funnel.

7. The checkers found it necessary to initiate the reaction with a crystal of iodine.

8. The submitters state that the purity of the product is greater than 98% by gas chromatographic analysis on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh and operated at 140°C . The retention time is about 4.7 min. An impurity with a retention time of about 2.9 min was detected. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 0.84 (s, 3 H), 0.88, (s, 3 H), 1.80-2.30 (m, 2 H), 2.69 (s, 1 H), 3.78 (d, 1 H, $J = 6$), 4.87-5.33 (m, 4 H), 5.57-6.13 (m, 2 H).

9. The copper complex is available from Strem Chemicals, Inc., under the name cuprous triflate (benzene complex). The checkers recommend handling the material in a dry box because of its high moisture and air sensitivity.

10. Anhydrous ether was distilled from lithium aluminum hydride under dry nitrogen immediately before use.

11. The submitters state that the copper(I) triflate is quite air stable in solution in the presence of the allylic alcohol.

12. The checkers recommend the use of a relatively new arc lamp. Substantially higher conversions were obtained with a new lamp because of an apparent bathochromic shift in the frequency of the light emitted as the lamp ages, thus lessening the intensity of light in the important absorption region for the reaction.

13. The submitters state that the purity of the product is greater than 97% by GLC analysis on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh and operated at 140°C. The retention time is about 8.0 min. The only impurity is unreacted diene with a retention time of about 4.7 min. The product is an epimeric mixture. TLC analysis by the submitters on 0.25-mm silica gel with 20% ethyl acetate in hexane shows major (>90%) and minor (<10%) epimers with R_f values of 0.32 and 0.23 respectively. The epimers are separable by column chromatography on silica gel with ethyl acetate-hexane mixtures as eluting solvents. A 3.1-g portion of the distilled isomer mixture was chromatographed by the checkers on 475 g of silica gel (Silica Woelm TSC - activity III/30 mm) using 5% ethyl acetate/hexane as eluent. The elution proceeded as follows: 1520 mL, nil; 1440 mL, 2.7 g of endo isomer; 1400 mL, nil; 2010 mL, 0.20 g of exo isomer. Analysis of the ^1H NMR spectrum of the distilled product confirms that the reaction is greater than 90% stereoselective in favor of the endo epimer. The major epimer, 3.3-

dimethyl-endo-cis-bicyclo[3.2.0]heptan-2-ol, has the following spectral properties: ^1H NMR (CDCl_3) δ : 0.81 (s, 3 H), 1.13 (s, 3 H), 1.4-3.2 (m, 9 H), 3.66 (d, 1 H, $J = 6.7$); ^{13}CMR (CDCl_3) δ : 16.3 (t), 22.5 (q, CH_3), 26.0 (t), 27.8 (q, CH_3), 36.0 (d), 42.8 (d), 45.5 (t), 45.8 (s, C-3), 80.9 (d, C-2). The minor epimer, 3,3-dimethyl-exo-cis-bicyclo[3.2.0]heptan-2-ol, has the following spectral properties: ^1H NMR (CDCl_3) δ : 0.77 (s, 3 H), 1.08 (s, 3 H), 1.2-2.9 (m, 9 H), 3.80 (d, 1 H, $J = 4.6$); ^{13}CMR (CDCl_3) δ 20.7 (q, CH_3), 24.0 (t), 26.5 (q, CH_3), 27.1 (t), 34.6 (d), 45.6 (s, C-3), 45.8 (d), 46.7 (t), 88.7 (d, C-2).

14. Certified ACS grade acetone purchased from Fisher Scientific Company was used as received.

15. Eisenbraun, E. J. *Org. Synth. Coll. Vol. V* 1973, 310-314.

16. Initially a gummy green precipitate is formed which is difficult to stir magnetically. Eventually, however, the inorganic by-products become more fluid. The use of a mechanical stirrer may be desirable.

17. The submitters state that the distilled product is <98% pure by GLC on a 6.4-mm x 1.4-m column packed with 15% FFAP on Chromosorb W, 60-80 mesh, operated at 140°C. The relative retention time is 2.3 versus an unidentified impurity at 1.0. The distilled product has the following spectral properties: IR (neat) cm^{-1} : 2960 (vs), 2940 (vs) and 1735 (vs) and other weaker bands. ^1H NMR (CCl_4) δ : 0.92 (s, 3 H), 1.12 (s, 3 H), 1.4-3.0 (m, 8 H); ^{13}CMR (CDCl_3), δ : 22.7, 24.1, 25.6, 26.4, 31.0, 43.9, 44.2, 48.4, 224.7.

3. Discussion

This procedure illustrates a general method for the preparation of 2-hydroxybicyclo[3.2.0]heptanes by copper(I)-catalyzed photobicyclization of 3-hydroxy-1,6-heptadienes,² and a general route to the requisite dienes from allyl alcohols by conversion to 4-pentenals and treatment of the latter with vinyl Grignard reagents.

Compound 1, 2,2-dimethyl-4-pentenal, has been prepared by the Claisen rearrangement route³ described above and by reaction of isobutyraldehyde with allyl chloride in the presence of aqueous sodium hydroxide and a phase-transfer catalyst.⁴ Both routes are applicable to the synthesis of a variety of substituted 4-pentenals.

cis-Bicyclo[3.2.0]heptan-2-ols have been prepared by reduction⁵ of the corresponding cis-bicyclo[3.2.0]-heptan-2-ones which have been prepared by photocycloaddition of alkenes with 2-cyclopentenones.⁶ The synthetic strategy of the present procedure is complementary.

1. Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106.
2. Salomon, R. G.; Coughlin, D. J.; Easler, E. M. *J. Am. Chem. Soc.* **1979**, *101*, 3961-3963.
3. Brannock, K. C. *J. Am. Chem. Soc.* **1959**, *81*, 3379-3383.
4. Dietl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 1273-1275.
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6. For reviews, see the following. Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50-57; Bauslaugh, P. G. *Synthesis* **1970**, 287-300; de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41-47.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Numbers)

4-Pentenal, 2,2-dimethyl- (8,9); (5497-67-6)

p-Cymene (8); Benzene, 1-methyl-4-(1-methylethyl)- (9); (99-87-6)

1,6-Heptadien-3-ol, 4,4-dimethyl- (9); (58144-16-4)

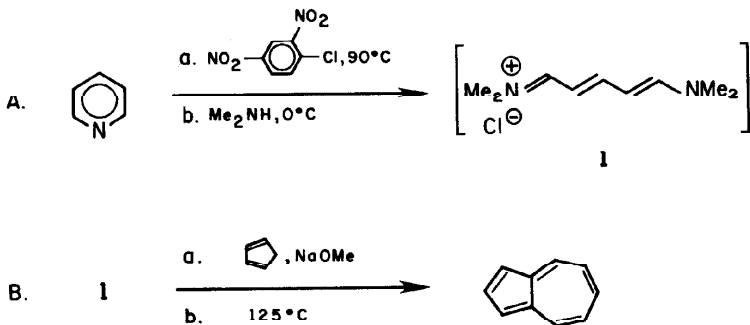
Ethylene, bromo-(8); Ethene, bromo- (9); (593-60-2)

Bicyclo[3.2.0]heptan-2-ol, 3,3-dimethyl- (9); (71221-67-5)

Bis(copper(I) trifluoromethanesulfonate)benzene complex: Copper,
(μ -(benzene))bis(trifluoromethanesulfonato-O)di- (9); (37234-97-2)

Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl- (9); (71221-70-0)

SYNTHESIS OF AZULENE



Submitted by Klaus Hafner and Klaus-Peter Meinhardt¹.

Checked by Stephen G. Senderoff and Andrew S. Kende.

1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, thermometer, and reflux condenser provided with a calcium chloride drying tube is charged with 202.6 g (1.0 mol) of 1-chloro-2,4-dinitrobenzene (Note 1) and 1.2 L of dry pyridine (Note 2). The mixture is heated while it is stirred in a water bath to 80–90°C for 4 hr. during which time a thick yellow precipitate of N-(2,4-dinitrophenyl)pyridinium chloride is formed (Note 3). After cooling to 0°C a solution of 100.0 g (2.22 mol) of dimethylamine in 300 mL of dry pyridine was pre-chilled to 0°C and added dropwise over a period of about 30 min with stirring. The resulting brownish-red liquid reaction mixture is allowed to

warm to room temperature and stirring is continued for 12 hr. The drying tube is replaced by a gas inlet and the system is flushed with dry nitrogen in a hood. Under nitrogen, 70.0 g (1.06 mol) of ice-cold, freshly-distilled cyclopentadiene (Note 4) is added, and subsequently 400 mL of 2.5 M sodium methoxide solution (Note 5) is slowly added dropwise to the stirred reaction mixture. During addition of the sodium methoxide, the temperature rises to 35-40°C. After the addition is completed, stirring is continued for another 4 hr. The reaction vessel is immersed in an oil bath, the dropping funnel removed, and the flask is fitted with a distillation head. The stirred mixture is cautiously heated under nitrogen (Note 6), and a mixture of pyridine and methanol is distilled off until the temperature of the reaction mixture has increased to 105-110°C (Note 7). After the distillation head is removed and 1 L of dry pyridine is added, the black mixture is heated with stirring under a nitrogen atmosphere for 4 days with a bath temperature of 125°C. It is then cooled to 60°C, the reflux condenser is replaced by a distillation head, and pyridine is removed under reduced pressure (Note 8). The gummy black solid residue is removed by a spatula and rinsed with hexanes. It is extracted in a Soxhlet apparatus with 1.5 L of hexanes in several batches. To remove the remaining pyridine, the combined blue hexane rinse and the extraction solutions are carefully washed with two 150-mL portions of 10% aqueous hydrochloric acid, then water (Note 9). The organic layer is dried with anhydrous sodium sulfate, the drying agent is removed by filtration, and the solvent is distilled through a 50-cm vacuum-jacketed Vigreux column. The crude azulene is purified by chromatography on activity II alumina (Note 10) with hexane, and yields azulene as blue plates, mp 96-97°C, yield 65-75 g (51-59%) (Note 11).

2. Notes

1. Commercial 1-chloro-2,4-dinitrobenzene was obtained from Aldrich Chemical Company, Inc. (Milwaukee) or from Bayer, AG (Leverkusen, FRG) and used directly.

2. Commercial pyridine was dried over potassium hydroxide or calcium hydride and distilled prior to use. The checkers used reagent grade pyridine (Mallinckrodt AR) which was distilled from KOH and stored over Linde 4A Molecular Sieves.

3. The reaction mixture should be evenly warmed to 80-90°C within 30 min with efficient mechanical stirring to prevent caking or "hot spots".

4. Dicyclopentadiene, obtained from the Aldrich Chemical Company, Inc. (or E. Merck, Darmstadt, FRG), was cracked just prior to use according to the procedure of Fieser and Williamson,² to give the monomer, bp 40-42°C.

5. Sodium methoxide was prepared just prior to use from 23.0 g (1.0 g-atom) of sodium metal and 400 mL of anhydrous methanol (distilled from magnesium turnings), then cooled to room temperature.

6. *Caution!* Dimethylamine is evolved.

7. Approximately 600 mL of distillate will be collected.

8. The blue pyridine distillate is redistilled through a 50-cm vacuum-jacketed Vigreux column (to avoid loss of azulene) until approximately 1.7 L is collected; the residual azulene is combined with the main residues for extraction.

9. A total volume of 2 L of hexane washes results, accompanied by the gradual precipitation of a yellow solid from the hexane washes. The acid-wash procedure frequently leads to emulsions and gummy yellow solid in both phases; back-extraction of the "aqueous" layer with hexane may be necessary.

10. Alumina was purchased from Macherey, Nagel and Co., Düren (FRG). The checkers employed 650 g of neutral alumina (Fisher, adsorption grade, 80-200 mesh) packed in a 40-cm high column. Yellow impurities remained on the column, while the blue azulene came off with the hexane solvent front.

11. Further purification of azulene may be achieved by sublimation at reduced pressure, mp 99°C.³ The checkers found that mechanical losses, particularly as mentioned in Note 9, lead to reduction in yield with reduction in scale (0.1 mol, 39% yield; 0.5 mol, 43% yield; 0.8 mol, 79% yield).

3. Discussion

Azulene has been synthesized by a variety of methods: by dehydrogenation of hydroazulenes,³ by annelation of a 7-membered ring on a 5-membered ring either by ring-closure of vinylogous aminopentafulvenes,^{4,5} or by cyclo-additions of aminopentafulvenes with activated 1,3-dienes or alkynes,⁶ and by annelation of a 5-membered ring on a 7-membered ring starting from troponoids or heptafulvenes.^{7,3b} Of these, the Ziegler-Hafner synthesis of azulene⁴ by thermal cyclization of the 6-(4-methylanilino-1,3-butadienyl)pentafulvene proved to be the most versatile. Azulene is also simply prepared from 6-dimethylaminopentafulvene and thiophene 1,1-dioxide or from 6-acyloxypentafulvenes and 1-diethylaminobutadiene, but with lower yields.^{6b,d,e}

The present procedure, based on the Ziegler-Hafner synthesis, is simple and avoids the use of benzidine for the ring-closure of the pentafulvene and isolation of the 5-dimethylamino-2,4-pentadienylidenedimethyliminium perchlorate.⁸ Other amines were also checked; with N-methylaniline ring-closure of the resulting pentafulvene in pyridine failed; with diethylamine a delay in boiling can take place during the reaction.

Substituted azulenes can be prepared in the same manner by the use of substituted cyclopentadienes or substituted pentamethinium salts.

1. Institut für Organische Chemie der Technischen Hochschule, Petersenstr. 22, D-6100 Darmstadt, (FRG).
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

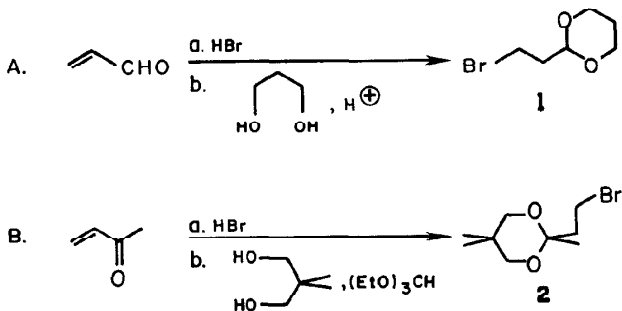
Azulene (8,9); (275-51-4)

1-Chloro-2,4-dinitrobenzene: Benzene, 1-chloro-2,4-dinitro- (8,9); (97-00-7)

Dimethylamine (8); Methanamine, N-methyl- (9); (124-40-3)

Dicyclopentadiene: 4,7-Methanoindene, 3a,4,7,7a-tetrahydro- (8); 4,7-Methano-
1-H-indene, 3a,4,7,7a-tetrahydro- (9); (77-73-6)

**β -HALOACETALS AND -KETALS: 2-(2-BROMOETHYL)-1,3-DIOXANE AND
2,5,5-TRIMETHYL-2-(2-BROMOETHYL)-1,3-DIOXANE**



Submitted by J. C. Stowell, D. R. Keith, and B. T. King¹.

Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. *2-(2-Bromoethyl)-1,3-dioxane* (1). A 2-L, three-necked flask is equipped with a mechanical stirrer, thermometer, and gas inlet tube. In the flask are placed 750 mL of dichloromethane, 112 g (2.00 mol) of acrolein (Note 1), and 0.10 g of dicinnamalacetone indicator (Note 2) under nitrogen. The yellow solution is cooled to 0-5°C with an ice bath. Gaseous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator becomes deep red (Note 4). The ice bath is removed and 1.0 g of *p*-toluenesulfonic acid monohydrate and 152.2 g (2.00 mol, 144 mL) of 1,3-propanediol (Note 1) are added. The yellow solution is stirred at room temperature for 8

hr, and then concentrated with a rotary evaporator. The residual oil is washed with two 250-mL portions of saturated aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Vacuum distillation through a 30-cm Vigreux column yields 252 g (65%) of **1** as a colorless liquid, bp 72-75°C (2.0 mm), n_D^{20} 1.4809 (Note 5).

B. *2,5,5-Trimethyl-2-(2-bromoethyl)-1,3-dioxane (2)*. A 1-L. three-necked flask is equipped with a magnetic stirrer and a gas inlet tube. In the flask are placed 700 mL of dichloromethane, 140 g (2.00 mol) of methyl vinyl ketone (Note 6), and 0.010 g of dicinnamalacetone indicator (Note 2). Anhydrous hydrogen bromide (Note 3) is bubbled into the solution with stirring until the indicator changes to deep red (Note 7). The gas inlet tube is removed and 208 g (2.00 mol) of neopentandiol, 296 g (2.00 mol) of triethyl orthoformate, and 0.67 g of p-toluenesulfonic acid monohydrate are added to the solution. The flask is stoppered and stirred at room temperature for 1-2 hr and then concentrated by rotary evaporation (Note 8). The concentrated solution is washed twice with saturated sodium bicarbonate solution (Caution: there is some foaming). The bicarbonate washes are extracted three times with dichloromethane and the combined organic portions dried over anhydrous K_2CO_3 . Rotary evaporation followed by vacuum distillation of the residue through a 30-cm Vigreux column yields 256 g (54%) of **2** as a clear, colorless oil, bp 65°C (0.3 mm), n_D^{22} 1.4687 (Note 9).

2. Notes

1. The acrolein, 1,3-propanediol, and cinnamaldehyde were purchased from Aldrich Chemical Company, Inc.

2. The indicator was prepared by the method of Diehl and Einhorn.² A solution of 5 g of sodium hydroxide in 50 mL of water and 40 mL of ethanol is prepared in a 250-mL Erlenmeyer flask. To this is added a solution of 1.84 mL (0.025 mol, 1.45 g) of acetone in 6.3 mL (0.050 mol, 6.6 g) of freshly distilled cinnamaldehyde (Note 1). This mixture is stirred thoroughly at room temperature for 30 min. The resulting voluminous yellow precipitate is filtered with suction, washed with 100 mL of water, and dried, affording 6.5 g of 1,9-diphenylnona-1,3,6,8-tetraen-5-one. Recrystallization from 200 mL of hot 95% ethanol gives 3.5 g of yellow crystals, mp 142-143°C (lit² mp 142°C). This indicator is also available from Aldrich Chemical Co.

3. The anhydrous hydrogen bromide was purchased in a lecture bottle from Matheson. A trap is used between the lecture bottle and the gas inlet tube.

4. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 3-bromopropanal (60 MHz, CH₂Cl₂) δ : 3.04 (t, 2 H), 3.59 (t, 2 H), 10.67 (s, 1 H).

5. Product 1 has the following spectral characteristics: IR (neat) cm⁻¹: 2980, 2870, 1250, 1150, 1140, 1015; ¹H NMR (90 MHz, CDCl₃) δ : 1.38 (d of m, 1 H, one 5-position on dioxane ring), 1.8-2.4 (m, the other 5-position on the dioxane ring), 2.14 (d of t, 2 H, CH₂-C-Br), 3.45 (t, 2 H, CH₂Br), 3.80 (d of t, 2, 4, and 6-positions on ring), 4.15 (d of double d, 2, 4, and 6-positions on ring), 4.71 (t, 1 H, 2-position on ring; ¹³C magnetic resonance (22.5 MHz, CDCl₃) δ : 100.06, 66.86, 38.08, 27.79, 25.79.

6. The neopentanediol and triethyl orthoformate were purchased from Aldrich Chemical Co., Inc. and used as received. Failure to distil the methyl vinyl ketone, also obtained from Aldrich Chemical Co., to a clear, colorless liquid before use resulted in difficulty in determining the endpoint of the reaction with HBr. Therefore, the methyl vinyl ketone was distilled prior to use at reduced pressure.

7. When the red color persists 5 min after the hydrogen bromide has been turned off, the addition is finished. At this point the proton magnetic resonance spectrum shows only dichloromethane and 4-bromo-2-butanone (60 MHz, CH_2Cl_2) δ : 2.15 (s, 3 H, CH_3CO), 3.02 (t, 2 H, CH_2CO), 3.52 (t, 2 H, CH_2Br); ^{13}C NMR (22.5 MHz, CDCl_3) δ : 25.75, 30.11, 45.91, 205.12. Little or no exotherm is noticed during the hydrogen bromide addition.

8. The reaction can be conveniently monitored by TLC using silica plates and eluting with 1:4 ethyl acetate-heptane.

9. Product 2 has the following characteristics: IR (neat liquid) cm^{-1} : 2970, 2880, 1260, 1220, 1125, 1085; ^1H NMR (60 MHz, CDCl_3) δ : 0.81 (s, 3 H, 5-methyl), 1.01 (s, 3 H, 5-methyl), 1.34 (s, 3 H, 2-methyl), 2.05-2.45 (m, 2 H, $\text{CH}_2\text{-C-Br}$), 3.2-3.8 (m, 6 H, CH_2O and CH_2Br); ^{13}C NMR (22.5 MHz, CDCl_3) δ : 19.64, 22.24, 22.76, 26.99, 29.72, 43.25, 70.23, 98.26.

3. Discussion

Cyclic β -haloacetals and -ketals have been prepared by variations on two basic methods. The most frequently used method involves the combination of an α,β -unsaturated carbonyl compound (acrolein, methyl vinyl ketone, crotonaldehyde, etc.) a diol, and the anhydrous hydrogen halide. All possible sequences of combining these three have been used. In most cases the

anhydrous acid was dissolved in the diol and then the carbonyl compound was added slowly.³⁻⁷ Alternatively, the acetals of the α,β -unsaturated carbonyl compounds were prepared and isolated and then the hydrogen halide was added.⁸ Finally the hydrogen halide may be added to the α,β -unsaturation followed by acetal formation,⁹ and this is the basis of the present procedures.

The second general method is the aluminum halide-catalyzed reaction of acid halides with ethylene to give β -halo ketones which are subsequently converted to ketals.^{10,11}

The preparations are much simplified if a stoichiometric amount of hydrogen halide is added using an indicator to determine the end point. We have found that 1,9-diphenylnona-1,3,6,8-tetraen-5-one (dicinnamalacetone)¹² is of appropriate basicity to detect excess anhydrous hydrogen halides in organic solvents including chloroform, dichloromethane, benzene, toluene, acetic acid, and acetone (but not in alcohols). The reaction between the hydrogen halide and the α,β -unsaturated carbonyl compound is fast enough at 0 to 25°C that the end point is readily detected, and the yield-lowering use of excess hydrogen halide or long contact times¹³ are avoidable. The intermediate β -halo aldehydes are unstable toward trimerization¹⁴ if they are not diluted by a solvent and therefore should not be isolated but used directly in the next step. β -Bromo ketones darken upon isolation and brief storage so they too should be protected directly.

The conversion of the intermediate bromo aldehyde to the dioxane proceeds readily owing to a favorable equilibrium position. However, the equilibrium for the reaction of the bromo ketone with the diol is unfavorable and requires removal of the by-product, water. This is done under mild conditions using ethyl orthoformate.¹⁵

We have chosen to use 1,3-diols because the Grignard reagents derived from the 1,3-dioxanes are thermally stable.¹⁶ This contrasts with the use of ethylene glycol where the resulting β -haloalkyl dioxolanes give Grignard reagents which decompose at 25 to 35°C.¹⁷⁻¹⁹ Acyclic acetals give insufficient protection to allow preparation of Grignard reagents.¹⁹ The protection of the ketone with 1,3-propanediol is not readily driven to completion, but with neopentanediol the equilibrium lies further toward ketal formation,²⁰ giving a better yield of more stable ketal.

β -Haloacetals and -ketals have recently seen wide use as alkylating agents^{10,21-24} and in the preparation of Grignard reagents. The Grignard reagents have been alkylated,²⁵ acylated,^{16,26} added to carbonyl groups,^{5,18,27-32} and used in Michael additions.³³⁻³⁵ One example also gives a useful Wittig reagent.⁹ Subsequent reactions of these products generally require removal of the acetal and ketal groups to regenerate the carbonyl function. This is readily done with aqueous acid in most cases, but not when aldehydes were protected with 1,3-diols because of the high equilibrium stability of the corresponding dioxanes. This problem is readily overcome by first converting to the dimethyl acetal in methanol and then using aqueous acid hydrolysis, or by using other specialized methods.^{9,16}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-(2-Bromoethyl)-1,3-dioxane: m-Dioxane, 2-(2-bromoethyl)- (8); 1,3-Dioxane, 2-(2-bromoethyl)- (9); (33884-43-4)

Acrolein (8); 2-Propenal (9); (107-02-8)

Dicinnamalacetone: 1,3,6,8-Nonatetraen-5-one, - 1,9-diphenyl (8,9); (622-21-9)

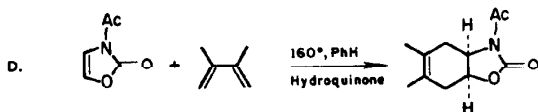
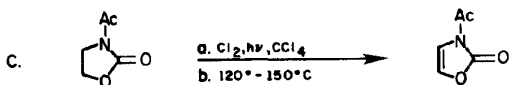
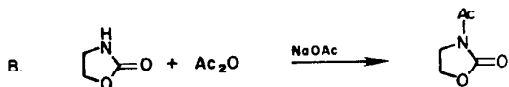
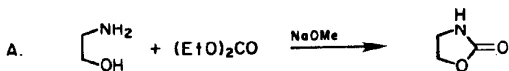
1,3-Propanediol (8,9); (504-63-2)

Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

4-Bromo-2-butanone: 2-Butanone, 4-bromo- (8,9); (28509-46-8)

Neopentanediol: 1,3-Propanediol, 2,2-dimethyl- (8,9); (126-30-7)

SYNTHESIS AND DIELS-ALDER REACTIONS OF 3-ACETYL-2(3H)-OXAZOLONE
[2(3H)-Oxazolone, 3-acetyl-]



Submitted by Karl-Heinz Scholz, Hans-Georg Heine, and Willy Hartmann¹.

Checked by Ashok B. Shenvi, Bruce M. Monroe, Richard E. Benson,
and Bruce E. Smart

1. Procedure

A. *2-Oxazolidinone*. A 2-L, three-necked flask equipped with a thermometer, magnetic stirring bar, and a Vigreux column fitted with a distillation head is charged with 305 g (5.0 mol) of freshly distilled 2-aminoethanol, 730 g (6.2 mol) of diethyl carbonate, and 2.5 g (0.05 mol) of sodium methoxide (Note 1). The mixture is stirred and the flask is heated in an oil bath maintained at 125-130°C. Ethanol begins to distill off when the internal temperature reaches 95-100°C. After heating for about 8 hr, the internal temperature reaches 125°C and ethanol ceases to distill (Note 2). The reaction mixture is allowed to cool to 60-70°C and is poured into 1 L of cold chloroform (Note 3). The resulting solution is chilled thoroughly in an ice-water bath and the precipitated product is recovered by filtration. The filtrate is concentrated to 250 mL and chilled to give a second crop. The combined crops are dried in a vacuum oven at 50°C to give 320-339 g (74-78%) of white crystals, mp 86-88°C [lit.² mp 87-89°C] (Note 4).

B. *3-Acetyl-2-oxazolidinone*. A 3-L, one-necked flask equipped with a reflux condenser and a magnetic stirring bar is charged with 326 g (3.75 mol) of 2-oxazolidinone, 94 g (1.15 mol) of anhydrous sodium acetate, and 1.6 L of acetic anhydride. The stirred solution is refluxed for 3 hr and the acetic anhydride is then removed by distillation at 15-20 mm. The residue is extracted with three 875-mL portions of boiling toluene (Note 5), and the hot toluene extractions are filtered, combined, and concentrated to a total volume of 675 mL. Diethyl ether (675 mL) is added with stirring to the toluene solution and the mixture is chilled in an ice-water bath. The precipitate is removed by filtration and washed with 250 mL of diethyl ether to give 328-403 g (68-83%) of colorless to very light tan crystals, mp 65-67°C [lit.² mp 69-

70°C] (Note 6). A second crop of 63-24 g (13-5%), mp 65-68°C, is obtained by concentrating the filtrate to 275 mL and chilling it in an ice-water bath.

C. *3-Acetyl 4- and 5-chloro-2-oxazolidinone*. A 3-L, four-necked flask is equipped with a reflux condenser topped with a gas discharge tube, thermometer, fritted glass inlet tube extending to the bottom of the flask, and a glass sleeve for accepting an UV lamp (Note 7). The reaction vessel is charged with 258 g (2.0 mol) of 3-acetyl-2-oxazolidinone, 2 L of carbon tetrachloride, and several boiling chips. The mixture is heated to gentle reflux, the light source is turned on, and 155 g (2.18 mol) of chlorine gas (Note 8) is introduced at such a rate that no chlorine escapes from the condenser (Note 9). After the addition is complete, heating is discontinued and nitrogen is bubbled through the reaction mixture to remove the dissolved hydrogen chloride. The solvent is then removed on a rotary evaporator to give a yellow oil, which consists of a mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinones³ and is used in Step D without further purification.

D. *3-Acetyl-2(3H)-oxazolone*. The crude mixture of 3-acetyl 4- and 5-chloro-2-oxazolidinone from Step C is placed in a 2-L, three-necked flask equipped with a thermometer, sealed mechanical stirrer, and gas discharge tube. The material is heated to 120°C with stirring, and the temperature is then slowly increased to 150°C and held there until the evolution of gas ceases (Note 10). The cooled, black reaction mixture is distilled at 20 mm. The fractions boiling up to 150°C are collected and redistilled through a 50-cm x 3-cm Vigreux column fitted with a variable take-off head. There is obtained 140-172 g (55-68%) of product, bp 108-112°C (24 mm), which solidifies, mp 35-37°C (Note 11).

E. *4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one*. A

solution of 63.5 g (0.5 mol) of 3-acetyl-2(3H)-oxazolone, 27.5 g (0.33 mol) of 2,3-dimethylbutadiene (Note 12) and 2.0 g of hydroquinone in 125 mL of benzene is heated at 160°C under nitrogen in a 360-mL Hastelloy C shaker tube (Note 13). After 12 hr, the pressure vessel is cooled to room temperature, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated another 12 hr at 160°C. The vessel is again cooled, recharged with 27.5 g of 2,3-dimethylbutadiene, and heated at 160°C for a final 12 hr. The resulting mixture is distilled to give 36.4-40.3 g (35-39%) of crude product, bp 115-130°C (0.5 mm), which solidifies (Notes 14 and 15). This material can be recrystallized by adding 36.4 g of melted product to 50 mL of boiling hexane, followed by cooling to give 27.6 g (26%) of crystals, mp 72-78°C (Note 16).

F. *6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol*. A solution of 26.1 g (0.125 mol) of 4-acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one and 42.0 g (0.75 mol) of potassium hydroxide in 200 mL of methanol and 100 mL of water is refluxed for 36 hr. The resulting mixture is exhaustively extracted with diethyl ether using a liquid-liquid continuous extraction apparatus. The ethereal extract is concentrated on a rotary evaporator and the residue is taken up in 150 mL of methylene chloride. The resulting solution is dried over anhydrous sodium sulfate, the drying agent is removed by filtration, and the filtrate is concentrated to dryness. The solid residue (16.5 g) is recrystallized from 100 mL of diethyl ether to give 11.2 g (64%) of colorless crystals, mp 63-65.5°C. A second crop of 2.3 g (13%) is obtained by concentrating the mother liquor to 50 mL and chilling in an ice-water bath (Note 17).

2. Notes

1. The checkers obtained 2-aminoethanol, diethyl carbonate, and anhydrous sodium methoxide from the Aldrich Chemical Company.

2. About 625 mL (theoretical: 583 mL) of ethanol is collected. If the reaction is stopped before this volume is collected, the yield is reduced.

3. If the reaction mixture cools below 60°C, the product solidifies in the flask.

4. The product shows the following ^1H NMR spectrum (d_6 -DMSO) δ : 3.3-3.8 (m, 2 H), 4.2-4.6 (m, 2 H), 6.5-7.5 (br s, 1 H) and is analytically pure. Anal. Calcd for $\text{C}_3\text{H}_5\text{NO}_2$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.61; H, 5.70; N, 16.06. The submitters report that they obtained pure material, mp 89-90°C, after three recrystallizations from chloroform.

5. This is conveniently done by adding the toluene to the residue in the flask, heating to reflux in an oil bath and then filtering the hot mixture.

6. This material shows the following ^1H NMR spectrum (CDCl_3) δ : 2.49 (s, 3 H), 3.8-4.7 (complex m, 4 H) and has acceptable analysis. Anal. Calcd for $\text{C}_5\text{H}_7\text{NO}_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.49; H, 5.40; N, 10.99. The submitters report that they obtained colorless, analytically pure material, mp 69-70°C, after three recrystallizations from benzene.

7. The submitters used a Philips HPK 125-watt high-pressure mercury vapor lamp. The sleeve is 2-mm Pyrex glass with an NS45 ground joint. The lamp does not require cooling. The checkers obtained equally good results by shining a Westinghouse 250-watt sun lamp on the reaction flask from a distance of 25 cm.

8. The chlorine gas is passed successively through three wash bottles. The center bottle is filled with concentrated sulfuric acid and the other two are left empty to serve as safety traps.

9. The photochlorination takes 4-6 hr. The hydrogen chloride evolved is absorbed in water.

10. Dehydrochlorination begins at about 120°C. The temperature is raised about 10°C/hr to 150°C to avoid vigorous gas evolution. The elimination of hydrogen chloride is complete after 5-6 hr.

11. The submitters report yields of 150-200 g, and that analytically pure material boils at 110°C (24 mm) and melts at 35-37°C after recrystallization from diethyl ether. The material obtained by the checkers showed a satisfactory analysis without further purification. Anal. Calcd for $C_5H_5NO_3$: C, 47.25; H, 3.97; N, 11.02. Found: C, 46.81; H, 4.00; N, 11.21. The material shows the following 1H NMR spectrum ($CDCl_3$) δ : 2.63 (s, 3 H), 6.90 (d, 1 H, $J = 2.5$), 7.30 (d, 1 H, $J = 2.5$); IR (CCl_4) cm^{-1} : 1880, 1735 (C=O).

12. The sample of 2,3-dimethylbutadiene was obtained from the Aldrich Chemical Company.

13. The submitters employed a nickel autoclave and noted that product from Step D may contain a small amount of hydrogen chloride or chlorinated material that can adversely affect a stainless steel pressure vessel. Hastelloy C is a high-nickel alloy.

14. The submitters obtained 48.0 g of product and 33.5 g of recovered starting material, bp 110°C (24 mm). The checkers found that the forerun collected at 108-112°C (24 mm) contained starting material, but it was highly contaminated with unidentified by-products.

15. The checkers obtained erratic results in this step, possibly because of surface effects or trace impurities in the pressure vessel. In two other runs, only 16.8-18.8 g of crude product were obtained. In one case, high boiling oligomers were formed, but none of the desired product was produced. Impurities in the diene or dienophile did not appear to be the problem since runs which employed recrystallized 3-acetyl-2(3H)-oxazolone and redistilled 2,3-dimethylbutadiene also gave variable results.

16. The submitters report pure product with bp 135-137°C (1.2 mm) and mp 78-80°C after recrystallization from chloroform. The checkers found that recrystallization from chloroform gave very poor recovery of product with mp 75-78°C. Material with mp 72-78°C is pure by NMR, mass spectroscopy, and combustion analysis; ^1H NMR (CDCl_3) δ : 1.70 (s, 6 H), 2.33 (m, 4 H), 2.45 (s, 3 H), 4.40 (d of t, 1 H, $J = 9.0, 4.5$), 4.83 (d of t, 1 H, $J = 9.0, 4.5$); IR (KBr) cm^{-1} : 1780, 1690. Mass spectrum m/e calculated: 209.1051. Found: 209.1030. Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.10; N, 6.67.

17. The product shows the following ^1H NMR spectrum (CDCl_3) δ : 1.60 (s, 6 H), 2.13 (br m, 4 H), 2.30 (s, 3 H), 3.00 (m, 1 H), 3.80 (m, 1 H) and is analytically pure. Anal. Calcd for $\text{C}_8\text{H}_{15}\text{ON}$: C, 66.35; H, 10.71; N, 9.92. Found: C, 66.17; H, 10.48; N, 10.26.

3. Discussion

The dienophile, 3-acetyl-2(3H)-oxazolone⁴, is an attractive intermediate for the synthesis of vicinal aminoalcohols with cis configurations. It reacts with 1,3-dienes, even under quite mild conditions, to form (4+2) cycloadducts.^{5,6} Its high reactivity with deactivated 1,3-dienes is noteworthy. This property is present also in 2(3H)-oxazolone⁴ which can be obtained easily through solvolysis of 3-acetyl-2(3H)-oxazolone in methanol. 3-Acetyl-2(3H)-oxazolone, on UV irradiation in the presence of a sensitizer, combines easily with olefins to form (2+2) cycloadducts,⁷ the hydrolysis of which leads to the class of cis-2-aminocyclobutanol.

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Appendix

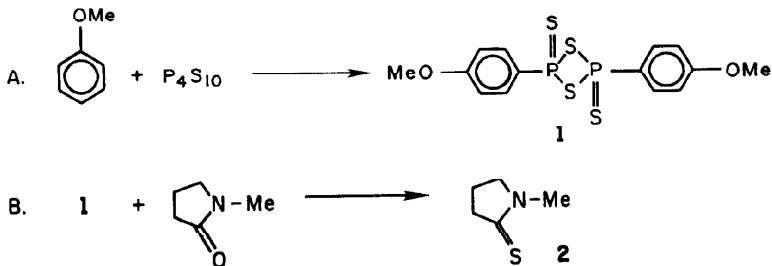
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 2-Aminoethanol: Ethanol, 2-amino- (8,9); (141-43-5)
- Diethyl carbonate: Carbonic acid, diethyl ester (8,9); (105-58-8)
- 2-Oxazolidinone (8,9); (497-25-6)
- 3-Acetyl-2-oxazolidinone: 2-Oxazolidinone, 3-acetyl- (8,9); (1432-43-5)
- 3-Acetyl-5-chloro-2-oxazolidinone: 2-Oxazolidinone, 3-acetyl-5-chloro- (9); (60759-48-0)
- 3-Acetyl-2(3H)-oxazolone: 2(3H)-Oxazolone, 3-acetyl- (9); (60759-49-1)
- 2,3-Dimethylbutadiene: 1,3-Butadiene, 2,3-dimethyl- (8,9); (513-81-5)
- Hydroquinone (8); 1,4-Benzenediol (9); (123-31-9)
- 4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one:
2(3H)-Benzoxazolone, 3-acetyl-3a,4,7,7a-tetrahydro-5,6-dimethyl- (9); (65948-43-8)
- 6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol: 3-Cyclohexen-1-ol, 6-amino-3,4-dimethyl-, cis- (9); (65948-45-0)

THIATION WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE

2,4-DISULFIDE: N-METHYLTHIOPYRROLIDONE

(2-Pyrrolidinethione, 1-methyl)



Submitted by I. Thomsen, K. Clausen, S. Scheibye, and S.-O. Lawesson¹.

Checked by Clayton H. Heathcock, Mark Sanner and Terry Rosen.

1. Procedure

Caution! Preparation of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide must be carried out in an efficient hood because hydrogen sulfide is evolved.

A. 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (1). A dry 1 L, three-necked, round bottomed flask, fitted with a reflux condenser, mechanical stirrer, and ground-glass stopper, is charged with 111.0 g (0.25 mol) of phosphorus sulfide, P_4S_{10} (Note 1) and 270 g (2.5 mol) of anisole (Note 1). Stirring is commenced and the mixture is heated at reflux temperature by use of a heating mantle. After 1 hr, the solution is

homogeneous and after a second hour 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (1) begins to precipitate. The reaction mixture is allowed to cool to room temperature and the precipitate is filtered (Note 2) and washed with anhydrous ether (2 x 50 mL) and 50 mL of anhydrous chloroform (free of alcohols) to yield 160-165 g (79-82%) of pale yellow crystals, mp 228°C (Notes 3 and 4).

B. *N*-Methylthiopyrrolidone (2). A 200-mL, three-necked, round-bottomed flask is fitted with a rubber septum, thermometer, magnetic stirring bar, and reflux condenser equipped with a nitrogen bubbler. The flask is charged with 19.8 g (19.3 mL, 0.20 mol) of *N*-methylpyrrolidone (Note 5) and 40.4 g (0.10 mol) of 1, whereupon the temperature of the reaction mixture increases to 75-80°C. After 5 min, 35 mL of benzene (Note 6) is added by syringe and the mixture is stirred while being brought to reflux (Note 7). The mixture is heated at reflux for 2 hr (Note 8) and then cooled to room temperature, whereupon it again becomes heterogeneous. The benzene is removed with the aid of a rotary evaporator and the resulting yellow slurry is distilled under reduced pressure through a 5-cm Vigreux column to provide 23.0 g (100%) of *N*-methylthiopyrrolidone (2) as a yellow liquid, bp 94-97°C/0.03 mm (Note 9).

2. Notes

1. Commercial phosphorus sulfide, P_4S_{10} , is used without purification. Checkers used P_4S_{10} from Matheson, Coleman and Bell and from Alfa Products, Morton/Thiokol, Inc. Best results (yield, melting point) were obtained with the Alfa sample, mp 291-295°C.

2. Excess anisole (137 g) can be recovered by distillation of the filtrate.

3. The product is somewhat hygroscopic and should be stored in an airtight container. It is also available as Lawesson's reagent from Aldrich, Fluka, and from Merck-Schuchard.

4. The checkers obtained 176 g (87%) of 1, mp 228-231°C.

5. Commercial material from the Aldrich Chemical Company was stored over 4Å molecular sieves.

6. Benzene was distilled from and stored over sodium wire.

7. During this operation most of the yellow solid gradually dissolves, affording a clear yellow solution with small amounts of suspended solid. When reflux begins, the internal temperature of the reaction mixture is 95°C.

8. The reaction time can be decreased to 3 min by the use of toluene as solvent.

9. The purified product freezes when stored in a refrigerator. The spectral properties are as follows: ^1H NMR (CDCl_3) δ : 2.07 (quintet, 2 H, $J = 7$), 3.03 (t, 2 H, $J = 7$), 3.29 (s, 3 H), 3.77 (t, 2 H, $J = 7$). IR (neat): 1520 cm^{-1} .

3. Discussion

A variety of thiating reagents are known: H_2S ,² $\text{H}_2\text{S}/\text{HCl}$,³ $\text{H}_2\text{S}_2/\text{HCl}$,⁴ $(\text{Et}_2\text{Al})_2\text{S}$,⁵ $(\text{EtAlS})_n$,⁶ SiS_2 ,⁷ B_2S_3 ,⁷ $\text{PCl}_5/\text{Al}_2\text{S}_3/\text{Na}_2\text{SO}_4$,⁸ $\text{Na}_2\text{S}/\text{H}_2\text{SO}_4$,⁹ P_2S_5 ,¹⁰ $\text{P}_2\text{S}_5/\text{pyridine}$,¹¹ $\text{P}_2\text{S}_5/\text{NEt}_3$,¹² $\text{P}_2\text{S}_5/\text{NaHCO}_3$,¹³ $\text{RPS}(\text{OR}^1)_2$,¹⁴ $\text{PSCl}_x(\text{NMe}_2)_{3-x}$ ($x = 0-3$),¹⁵ and SCNCOOEt .¹⁶ The reagent described here, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (1)¹⁷ offers a number of advantages as a thiating reagent. It is easily prepared in a simple one-step procedure employing commercially available starting materials. It has a satisfactory shelf life, provided that it is protected from moisture. In contrast to

commercial P_4S_{10} , compound 1 is a well-defined reagent which gives reproducible results, usually in high yield. Under defined conditions, certain selectivity has been observed.¹⁸⁻²⁰ Other methods for the preparation of analogs of 1 have been described.²¹⁻²³

The thiation procedure described here²⁴ is an example of a general synthetic method for the conversion of carbonyl to thiocarbonyl groups. Similar transformations have been carried out with ketones,²⁵ carboxamides,²⁶⁻³⁰ esters,³¹⁻³² thioesters,³¹ lactones,^{18,33} thiolactones,¹⁸ imides,²⁴ enaminones,³⁴ and protected peptides.³⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide: Phosphonotrithioic acid, (p-methoxyphenyl)-bimol cyclic anhydrosulfide (8);
1,3,2,4-Dithiaphosphetane, 2,4-bis(4-methoxyphenyl)- 2,4-disulfide (9);
19172-47-5

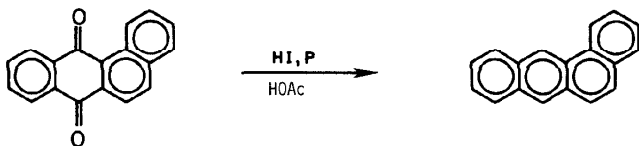
N-Methylthiopyrrolidone: 1-Methyl-2 (3H)-pyrrolothione, dihydro- (8);
2-Pyrrolidinethione, 1-methyl- (9); 10441-57-3

N-Methylpyrrolidone: 2-Pyrrolidinone, 1-methyl- (8,9); 872-50-4

Anisole (8); Benzene, methoxy- (9)- ; 100-66-3

Phosphorus sulfide (8,9); 12066-62-5

REDUCTION OF QUINONES WITH HYDRIODIC ACID: BENZ[a]ANTHRACENE



Submitted by Maria Konieczny and Ronald G. Harvey¹.

Checked by Gregory A. Reed and Carl R. Johnson.

1. Procedure

Caution! Benz[a]anthracene and benzene are known carcinogens. All appropriate precautions should be taken in handling these substances.

A 500-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and an efficient condenser, and charged with 10.3 g (0.04 mol) of benz[a]anthracene-7,12-dione (Note 1), 5 g (0.16 mol) of red phosphorus (Note 2) and 100 mL of glacial acetic acid. The stirred suspension is heated to reflux, and 60 mL of 56% hydriodic acid (approx. 0.44 mol) (Note 3) is introduced through the condenser. The suspension is heated at reflux for 24 hr. The hot reaction mixture is poured into 500 mL of distilled water containing ~ 30 g of sodium bisulfite. The suspension is stirred for 16 hr and filtered. The dry filter cake is transferred to a beaker and treated with sufficient hot dichloromethane (~ 120 mL) to dissolve all of the benz[a]anthracene, and the mixture is filtered once again to remove the residual phosphorus. The volume

of the filtrate is reduced to 40 mL. The solution is adsorbed on basic alumina, activity I (Note 4). A chromatography column (2-cm x 40-cm) is slurry-packed with ca. 10 g of basic alumina and the benz[a]anthracene adsorbed on alumina is added to the top of the column. Elution with 5% benzene in hexane (occasional rinsing of the column tip with benzene to remove crystallized product may be necessary) and evaporation of the solvent in a rotary evaporator affords 7.7-7.9 g (84-87%) of pure, white benz[a]anthracene, mp 159.5-160°C (Note 5).

2. Notes

1. Benz[a]anthracene-7,12-dione, available from Eastman Organic Chemicals, was used without further purification.

2. Phosphorus, which serves to scavenge the I_2 produced, can be omitted. However, the product tends to retain traces of a yellow impurity which is difficult to remove.

3. The hydriodic acid employed was a 56% aqueous solution preserved with ~ 0.8% hypophosphorous acid obtained from Fisher Scientific Co. Once a bottle is opened, the contents tend to deteriorate, becoming dark-colored in less than 2 days. However, shelf life can be extended indefinitely if the container is purged with dry nitrogen before resealing.

4. Alumina sufficient to adsorb the complete solution is added, then the solvent is removed under vacuum. While benz[a]anthracene, mp 157-158°C, sufficiently pure for most purposes, can be obtained by crystallization of the crude product from ethanol-water, "filtration" through alumina removes residual, colored impurities, affording a pure, white product.

5. Pure benz[a]anthracene has been reported to melt at 158-159°, ² 160°, ³ and 167°C. ⁴ The submitters report a mp of 164-164.5°C. The submitters conducted this preparation on a scale five times larger and reported yields up to 95%.

3. Discussion

The synthetic procedure described is based on that reported earlier for the synthesis on a smaller scale of anthracene, benz[a]anthracene, chrysene, dibenz[a,c]anthracene, and phenanthrene ⁵ in excellent yields from the corresponding quinones. ⁶ Although reduction of quinones with HI and phosphorus was described in the older literature, relatively drastic conditions were employed and mixtures of polyhydrogenated derivatives were the principal products. ⁷ The relatively milder experimental procedure employed herein appears generally applicable to the reduction of both ortho- and para-quinones directly to the fully aromatic polycyclic arenes. The method is apparently inapplicable to quinones having an olefinic bond, such as o-naphthoquinone, since an analogous reaction of the latter provides a product of undetermined structure (unpublished result). As shown previously, ⁶ phenols and hydroquinones, implicated as intermediates in the reduction of quinones by HI, can also be smoothly deoxygenated to fully aromatic polycyclic arenes under conditions similar to those described herein.

Although previous experience indicates that phosphorus is not essential for these reductions, ^{6,8} purification of the product is more difficult with its omission. With hydrocarbons sensitive to further reduction, phosphorus can have a deleterious effect through promotion of hydrogenation of the desired product. Whether or not phosphorus should be employed in an indi-

vidual case will be dictated by experience with the particular compound and by the degree of purity required.

While the reduction of polycyclic quinones to phenols, hydroquinones, dihydrodiols, dihydro arenes and arenes by a variety of reagents has been described, no entirely satisfactory general method is currently available for reduction directly to the fully aromatic arenes. Reagents previously employed for this purpose include LiAlH_4 ,^{9,10} NaBH_4 ,¹¹ $\text{NaBH}_4\text{-BF}_3$,^{11a,12} diborane,¹² aluminum and cyclohexanol,¹³ zinc dust distillation,¹⁴ and diphenylsilane.¹⁵ These methods commonly furnish lower yields and are less general than the present procedure.

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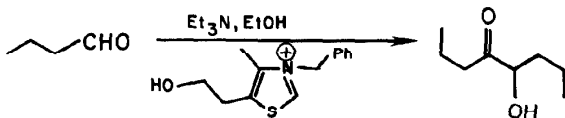
Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

Benz[a]anthracene (8,9); (56-55-3)
Benz[a]anthracene-7,12-dione (8,9); (2498-66-0)
Phosphorus (8,9); (7723-14-0)
Hydriodic acid (8,9); (10034-85-2)

ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS: BUTYROIN

(4-Octanone, 5-hydroxy-)



Submitted by H. Stetter and H. Kuhlmann¹.

Checked by Sharbil J. Firsan and Robert M. Coates.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube. The flask is charged with 13.4 g (0.05 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (Note 1), 72.1 g (1.0 mol) of butyraldehyde (Note 2), 30.3 g (0.3 mol) of triethylamine (Note 2), and 300 mL of absolute ethanol. A slow stream of nitrogen (Note 3) is begun, and the mixture is stirred and heated in an oil bath at 80°C. After 1.5 hr the reaction mixture is cooled to room temperature and concentrated by rotary evaporation. The residual yellow liquid is poured into 500 mL of water contained in a separatory funnel, and the flask is rinsed with 150 mL of dichloromethane which is then used to extract the aqueous mixture. The aqueous layer is extracted with a second 150-mL portion of

dichloromethane. The combined organic phases are washed with 300 mL of saturated sodium bicarbonate and with 300 mL of water. The dichloromethane is removed by rotary evaporation under slightly diminished pressure. Distillation through a 20-cm Vigreux column gives 51-54 g (71-74%) of product as a colorless to light yellow liquid, n_D^{20} 1.4309, bp 90-92°C (13-14 mm) (Notes 4 and 5).

2. Notes

1. The catalyst, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride, is supplied by Fluka AG, Buchs, Switzerland, and by Tridom Chemical, Inc., Hauppauge, New York. The thiazolium salt may also be prepared as described below² by benzylation of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole which is commercially available from E. Merck, Darmstadt, West Germany, and Columbia Organic Chemicals Co., Inc., Columbia, SC. The acetonitrile used by the checkers was dried over Linde 3Å molecular sieves³ and distilled under nitrogen, bp 77-78°C. The same yield of thiazolium salt was obtained by the checkers when benzyl chloride and acetonitrile from commercial sources were used without purification.

A 250-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube, and a stopper. The flask is charged with 14.3 g (0.1 mol) of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole, 12.7 g (0.1 mol) of freshly distilled benzyl chloride, and 50 mL of dry acetonitrile. The mixture is heated at reflux for 24 hr and cooled to room temperature. Crystallization is induced by scratching or seeding. The solid is collected by suction filtration, washed colorless with two 50-mL portions of acetonitrile, and dried partially in the air. Drying is

completed under reduced pressure by gentle rotation on a rotary evaporator heated with a water bath at about 90°C. The yield of thiazolium salt, mp 141-143°C, is 18.2-19.6 g (67-73%).

2. Butyraldehyde is supplied by Aldrich Chemical Co., Inc., and Eastman Organic Chemicals. The aldehyde was freshly distilled before use. Triethylamine was dried over potassium hydroxide pellets and distilled.

3. The submitters recommend that the nitrogen stream be passed through a bubbler and that the flow rate be adjusted to ca. one bubble per second. If the nitrogen flow is too fast, some of the butyraldehyde will be swept out of the flask.

4. The procedure may be conducted on a larger scale in which case the proportion of catalyst and base are reduced. The submitters report that they obtained 169 g (78%) of butyrolin from 216.3 g (3.0 mol) of butyraldehyde, 26.8 (0.1 mol) of thiazolium catalyst, 60.6 g (0.6 mol) of triethylamine, and 600 mL of absolute ethanol. Although the scale may be increased further, appropriate precautions should be taken to control the reaction. For example, the aldehyde may be added in portions or the flask may be cooled initially.

5. The product obtained by the checkers boiled at 86-87.5°C (15-16 mm). A boiling point of 85-87°C (12-13 mm) and an index of refraction n_D^{20} 1.4325 have been recorded for butyrolin.⁴ The product exhibits the following spectral characteristics: IR (neat) cm^{-1} : 3505 and 1704; ^1H NMR (CCl_4) δ : 3.98 (m, 1 H, CHOH), 3.31 (s, 1 H, OH), 2.41 (t, 2 H, J = 7, $\text{CH}_2\text{C=O}$), 1.64 (sextet, 2 H, J = 7, $\text{CH}_2\text{CH}_2\text{C=O}$), 1.56-1.18 (m, 4 H, 2 CH_2), 0.94 (unsymmetrical t, 6 H, 2 CH_3).

3. Discussion

This procedure is representative of a new general method for the preparation of noncyclic acyloins by thiazolium-catalyzed dimerization of aldehydes in the presence of weak bases (Table I).⁵ The advantages of this method over the classical reductive coupling of esters⁶ or the modern variation in which the intermediate enediolate is trapped by silylation,^{4,7} are the simplicity of the procedure, the inexpensive materials used, and the purity of the products obtained. For volatile aldehydes such as acetaldehyde and propionaldehyde the reaction is conducted without solvent in a small, heated autoclave. With the exception of furoin the preparation of benzoin from aromatic aldehydes is best carried out with a different thiazolium catalyst bearing an N-methyl or N-ethyl substituent, instead of the N-benzyl group.⁵ Benzoin has usually been prepared by cyanide-catalyzed condensation of aromatic and heterocyclic aldehydes.^{8,9,10} Unsymmetrical acyloins may be obtained by thiazolium-catalyzed cross-condensation of two different aldehydes.¹¹ The thiazolium ion-catalyzed cyclization of 1,5-dialdehydes to cyclic acyloins has been reported.¹²

Although the catalysis of the dimerization of aldehydes to acyloins by thiazolium ion has been known for some time,¹³ the development of procedures using anhydrous solvents which give satisfactory yields of acyloins on a preparative scale was first realized in the submitters' laboratories.⁵ The mechanism proposed by Breslow^{13a} for the thiazolium ion-catalyzed reactions is similar to the Lapworth mechanism¹⁴ for the benzoin condensation with a thiazolium ylide replacing the cyanide ion. Similar mechanisms are involved

in many important enzyme-catalyzed transformations which require thiamine as a co-factor. The combination of thiazolium salts and weak bases has also been utilized to catalyze the conjugate addition of aldehydes to electron-deficient double bonds.²

Butyrolin has been prepared by reductive condensation of ethyl butyrate with sodium in xylene,^{6b} or with sodium in the presence of chlorotrimethylsilane,⁷ and by reduction of 4,5-octanedione with sodium 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-sulfinate in the presence of magnesium chloride¹⁵ or with thiophenol in the presence of iron polyphthalocyanine as electron transfer agent.¹⁶ This acyloin has also been obtained by oxidation of (E)-4-octene with potassium permanganate¹⁷ and by reaction of propylmagnesium bromide with nickel tetracarbonyl.¹⁸

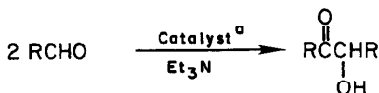
Acyloins are useful starting materials for the preparation of a wide variety of heterocycles (e.g., oxazoles¹⁹ and imidazoles²⁰) and carbocyclic compounds (e.g., phenols²¹). Acyloins lead to 1,2-diols by reduction, and to 1,2-diketones by mild oxidation.


1. Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule Aachen, West Germany.
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TABLE I
ACYLOINS PREPARED BY THIAZOLIUM ION-CATALYZED
CONDENSATION OF ALDEHYDES⁵



R	Yield(%)	Bp or mp (°C)
C ₄ H ₉	79	83 (2.2 mm)
C ₅ H ₁₁	81	90 (1.5 mm)
C ₇ H ₁₅	83 ^b	39
C ₉ H ₁₉	85 ^b	53
C ₁₁ H ₂₃	83 ^b	62
	80 ^{c,d}	136

^a3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride. ^bThe product was isolated by pouring the ethanolic solution into well-stirred, ice-cold water, filtering, and recrystallizing from aqueous ethanol. The solutions should be ice cold for the isolation of the low-melting acyloins. The products may also be isolated by extraction as described for butyrolin.

^cIn this case furoin crystallized from the ethanolic solution upon cooling.

^dThe following somewhat simpler procedure may also be used. A solution of 13.4 g (0.05 mol) of catalyst, 96.1 g (1.0 mol) of 2-furaldehyde, 300 mL of absolute ethanol, and 30.3 g (0.3 mol) of triethylamine is stirred at room temperature for 12 hr. The product (84.5 g, 88%) crystallizes directly from solution and is isolated by filtration.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Benzyl chloride: Toluene, α -chloro- (8); Benzene, (chloromethyl)- (9); (100-44-7).

Butyraldehyde (8); Butanal (9); (123-72-8)

Butyrolin: 4-Octanone, 5-hydroxy- (8,9); (496-77-5)

2-Furaldehyde (8); 2-Furancarboxaldehyde (9); (98-01-1)

5-(2-Hydroxyethyl)-4-methyl-1,3-thiazole: 5-Thiazoleethanol, 4-methyl- (8,9); (137-00-8)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride: Thiazolium,

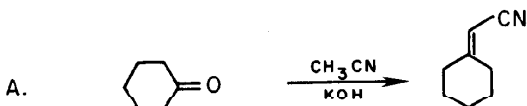
3-benzyl-5-(2-hydroxyethyl)-4-methyl-, chloride (8); Thiazolium,

5-(2-hydroxyethyl)-4-methyl-3-(phenylmethyl)-, chloride (9); (4568-71-2)

SYNTHESIS OF α,β -UNSATURATED NITRILES FROM ACETONITRILE:

PREPARATION OF CYCLOHEXYLIDENEACETONITRILE AND CINNAMONITRILE

(Acetonitrile, cyclohexylidene- and 2-Propenenitrile, 3-phenyl, (E)-)



Submitted by Stephen A. DiBiase, James R. Beadle, and George W. Gokel¹.

Checked by Yumi Nakagawa and Robert V. Stevens.

1. Procedure

A. *Cyclohexylideneacetonitrile.* A 1-L three-necked, round-bottomed flask equipped with a reflux condenser, mechanical stirrer and addition funnel, is charged with potassium hydroxide (85% pellets, 33.0 g, 0.5 mol, Note 1) and acetonitrile (250 mL, Notes 2 and 3). The mixture is brought to reflux and a solution of cyclohexanone (49 g, 0.5 mol, Note 4) in acetonitrile (100 mL) is added over a period of 0.5-1.0 hr. Heating at reflux is continued for 2 hr (Note 5) after the addition is complete and the hot solution is then poured onto cracked ice (600 g). The resulting binary mixture is separated

and the aqueous phase is extracted with ether (3 x 200 mL). The combined organic extracts are evaporated under reduced pressure, or may be placed in a 2-L Erlenmeyer flask containing several boiling chips and the volume reduced on a steam bath (internal temperature ca. 50°C). The resulting sweet-smelling, yellow to yellow-orange oil is transferred to a 1- or 2-L, three-necked, round-bottomed flask (depending on whether internal or external steam generation is used) and steam distilled (bp 81-99°C, Note 6). The distillate is extracted with three to five 200-mL portions of ether until the aqueous phase is clear (Note 7). The ether phase is washed with brine (2 x 100 mL), dried over sodium sulfate and evaporated under reduced pressure to give a pale yellow oil (29-36 g, 48-60%) which consists of a mixture of isomers (α,β 80-83%, β,γ 17-20%, Note 8).

Isolation of the pure α,β isomer. A 250-mL Erlenmeyer flask equipped with a magnetic stirring bar is charged with the isomeric nitriles (20 g, 0.165 mol), prepared in Part A above, and carbon tetrachloride (20 mL). A solution of bromine in carbon tetrachloride (1/9, v/v, ca. 25-30 mL) is added dropwise until the color of excess bromine persists. The reaction vessel is cooled in an ice bath for 30 min, filtered by gravity and the solvent evaporated under reduced pressure. The crude oil is distilled at reduced pressure (bp 40-42°C/0.15 mm) to give a colorless liquid (11-15 g, 55-75%) which is the pure α,β -isomer (Notes 9 and 10).

B. Preparation of E- and Z-Cinnamonnitrile. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel is charged with potassium hydroxide pellets (33 g, 0.5 mol, Note 1) and acetonitrile (400 mL, Note 2). The mixture is brought to reflux under nitrogen and a solution of benzaldehyde (53 g, 0.5 mol, Note 4) in acetonitrile (100 mL) is added in a stream (1-2 min). After addition,

stirring is continued for 10 min (Note 5) and the hot solution is then poured onto 500 g of cracked ice in a 1-L beaker. After being cooled for a few minutes, the two-phase mixture is transferred to a 2-L, three-necked flask and steam distilled (Note 11). The distillate is transferred to a separatory funnel, the upper aqueous phase is separated and then extracted with two 500-mL portions of ether (Note 7). The combined organic material is dried briefly over Na_2SO_4 and the ether evaporated to yield pure cinnamonnitrile (20-29 g, 31-45%) as a pale yellow oil (E/Z ratio ca. 5.5, Note 12).

2. Notes

1. Potassium hydroxide (85% pellets, AR grade) should be as fresh as possible (see Note 5).

2. Acetonitrile (99%) was obtained from Aldrich Chemical Company, Inc. and may be used without purification.

3. The yield of product is dependent on concentration. An increase in the amount of acetonitrile in Part A to ca. 1000 mL increases the yield of the isomer mixture to 65-75% without affecting isomer distribution. Further dilution to ca. 5000 mL increases the yield to 80-85%.

4. Cyclohexanone and benzaldehyde were purchased from either Aldrich Chemical Company, Inc., or Eastman Organic Chemicals and used without additional purification.

5. The reaction time depends on the quality of the potassium hydroxide employed. An induction period is often observed when older potassium hydroxide samples are used, possibly because surface formation of carbonates reduces the solubility of the salt in acetonitrile. An attempt was made to monitor the cinnamonnitrile reaction by GLC, following loss of starting

material. Although formation of the product was observed and reached a maximum, the starting material peak never completely disappeared. Prolonged reaction times (greater than 2 hr) resulted in failure to isolate any of the desired product. Reaction times of less than 30 min gave the expected yields. Undissolved potassium hydroxide was observed in the reaction vessel when these reactions were terminated. At a column temperature of 150°C and a gas flow rate of ca. 60 mL/min (5-ft x 0.25-in column, 10% SE-30 on fire-brick), the retention times are as follows: cyclohexylideneacetonitrile and isomer, 2.8 min; Z-cinnamitrile, 3.0 min; E-cinnamitrile, 3.7 min). The reaction may also be monitored by a 2,4-dinitrophenylhydrazine spot test.

6. Distillation may be conducted using an apparatus designed either for internal or external steam generation. The first 1000-ml. portion of distillate contains ca. 35 g of product. An additional 500 mL of distillate yields less than 1 g. Vacuum distillation gave product in 22% yield.

7. To facilitate phase separation, solid sodium chloride was added to the aqueous layer.

8. The product thus obtained is of high purity. The trace of color may be removed by distillation at reduced pressure (bp 50°C/0.5 mm).

9. Bromination can be monitored by ^1H NMR in CCl_4 . The vinyl protons are observed at 5.08 (α,β -isomer) and 5.65 ppm.

10. The ^1H NMR spectra (in CCl_4) for the two isomers are as follows: Cyclohexylideneacetonitrile: δ 1.25-2.0 (m, 6 H), 2.0-2.8 (m, 4 H, methylene protons), 5.08 (m, 1 H, olefin); 2-(1-cyclohexenyl)acetonitrile: 1.25-2.0 (m, 4 H), 2.0-2.8 [m, 4 H, $-(\text{CH}_2)_4-$], 3.05 (pseudo-s, 2 H, $-\text{CH}_2\text{CN}$), 5.65 (m, 1 H, olefin).

11. Steam distillation may be conducted using apparatus designed either for internal or external steam generation. Using internally-generated steam, 2.5 L of distillate was collected. The last 500 mL contained less than 1 g of product.

12. Isomer distribution and purity were assessed by GC (see Note 5). The ^1H NMR spectra (in CCl_4) for the pure isomers are as follows: E-isomer: δ 5.71 (d, 1 H, $J = 17$, $\text{ArCH}=\text{CH}-\text{CN}$); 7.44 (d, 1 H, $J = 17$, $\text{ArCH}=\text{CHCN}$), 7.3 (pseudo-s, 5 H, aromatic protons). Z-isomer: δ 5.31 (d, 1 H, $J = 12$, $\text{ArCH}=\text{CHCN}$), 6.98 (d, 1 H, $J = 12$, $\text{ArCH}=\text{CHCN}$), 7.3 (pseudo-s, 5 H, aromatic protons).

3. Discussion

Introduction of the two-carbon fragment is a cornerstone of synthetic methodology and many of the condensation reactions frequently used have been known for decades, if not for a century. Examples include the malonic ester² and acetoacetic ester³ reactions, the Perkin⁴ condensation, and the Doebner-Knoevenagel⁵ reaction. Addition of the cyanomethyl group has been accomplished by a variety of methods,⁶ mostly circuitous, and is certainly not in the group of classical reactions named above. The direct approach is found in a recent application of lithio trimethylsilylacetonitrile,⁷ but the difference in expense and convenience between using this method and a mixture of potassium hydroxide and acetonitrile is manifest.

The direct synthesis of α,β -unsaturated nitriles can be accomplished by treating the appropriate carbonyl compound with potassium hydroxide in acetonitrile.⁸ In order for direct condensation to succeed, acetonitrile must be deprotonated by the relatively weak base potassium hydroxide and the carbanion thus formed must add to the carbonyl. The cyanohydrin is presumably

dehydrated to leave the α,β -unsaturated compound which may or may not isomerize in the medium. We have run this reaction with a large number of carbonyl compounds⁸ and have found that it is most successful for aromatic aldehydes (36-86%) and other nonenolizable carbonyl compounds such as benzophenone (84%). Yields are also acceptable for most cyclic ketones with six or more carbons in the ring (e.g., 2-methylcyclohexanone, 78%; cis-octalone, 80%; cycloheptanone, 78%; cyclooctanone, 66%, cyclododecanone, 4-5%), and for aliphatic ketones having three or more carbons bonded on each side (e.g., diethyl ketone, 35%; di-n-propyl ketone, 65%, di-n-butyl ketone 6-5%). Ketones which are sterically hindered (camphor) or highly enolized (cyclopentanone) are not useful substrates in this reaction.

We present here examples of this condensation with an aromatic aldehyde and a cyclic ketone. Both of these examples are useful because, although other methods are available for their preparation, problems often attend these syntheses. In the synthesis of cyclohexylideneacetonitrile, for example, the standard method⁹ results exclusively in the β,γ -isomer and none of the α,β -isomer. In Part A of this procedure, cyclohexanone is condensed with acetonitrile to give predominantly the conjugated isomer (80-83%) which is then separated from the nonconjugated isomer by selective bromination.

The procedures presented here are simple, inexpensive, and may be used on a large scale. The use of potassium hydroxide in this reaction may, however, prove incompatible with certain base-sensitive functional groups.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclohexylideneacetonitrile: $\Delta^{1,\alpha}$ -Cyclohexaneacetonitrile (8); Acetonitrile, cyclohexylidene (9); (4435-18-1)

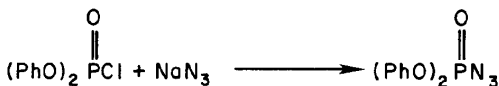
Cinnamonnitrile (8); 2-Propenenitrile, 3-phenyl-, (E)- (9); (1885-38-7)

Cyclohexanone (8,9); (108-94-1)

Acetonitrile (8,9); (75-05-8)

Benzaldehyde (8,9); (100-52-7)

DIPHENYL PHOSPHORAZIDATE
(Phosphorazidic acid, diphenyl ester)



Submitted by Takayuki Shioiri¹ and Shun-ichi Yamada².

Checked by Christina Bodurow and M. F. Semmelhack.

1. Procedure

A mixture of 56.8 g (0.21 mol) of diphenyl phosphorochloridate (Note 1), 16.3 g (0.25 mol) of sodium azide, and 300 mL of anhydrous acetone (Note 2) in a 500-mL round-bottomed flask fitted with a calcium chloride tube is stirred at 20–25°C for 21 hr. The lachrymatory mixture is filtered in a hood, and the filtrate is concentrated under reduced pressure. The residue is distilled through a short Vigreux column (Note 3). The yield of diphenyl phosphorazidate, bp 134–136°C (0.2 mm), is 49–52 g (84–89%) (Note 4).

2. Notes

1. Diphenyl phosphorochloridate (diphenyl chlorophosphate), from Aldrich Chemical Company, Inc., was used after purification by distillation at 165–168°C (5 mm).

2. Commercial acetone was dried over anhydrous potassium carbonate and distilled.

3. The bath temperature should be kept below 200°C to minimize decomposition of diphenyl phosphorazidate.³

4. Diphenyl phosphorazidate is a colorless non-explosive oil that can be kept for a long time without decomposition if it is protected against light³ and moisture.

3. Discussion

The procedure described is essentially that of Shioiri and Yamada.⁴ Diphenyl phosphorazidate is a useful and versatile reagent in organic synthesis.⁵ It has been used for racemization-free peptide syntheses,^{4,6,7} thiol ester synthesis,⁸ a modified Curtius reaction,^{6,9,10} an esterification of α -substituted carboxylic acid,¹¹ formation of diketopiperazines,¹² an alkyl azide synthesis,¹³ phosphorylation of alcohols and amines,¹⁴ and polymerization of amino acids and peptides.¹⁵ Furthermore, diphenyl phosphorazidate acts as a nitrene source³ and as a 1,3-dipole.^{16,17} An example in the ring contraction of cyclic ketones to form cycloalkanecarboxylic acids is presented in the next procedure, this volume.

1. Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya 467, Japan.
2. Faculty of Pharmaceutical Sciences, Josai University, Saitama 350-02, Japan.
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4. Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 849. No spectral and/or analytical data appear to have been reported for diphenyl phosphorazidate. The checkers recorded the following spectral data: ^1H NMR (CDCl_3), δ : 7.0-7.3 (br, s, C_6H_5 -); IR (neat) cm^{-1} : 3060 (w, C-H), 2170 (s, $-\text{N}_3$), 1590 (m), 1490 (s, arene C=C), 1270 (m, P=O), 960 (s, P-O-aryl).
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Appendix

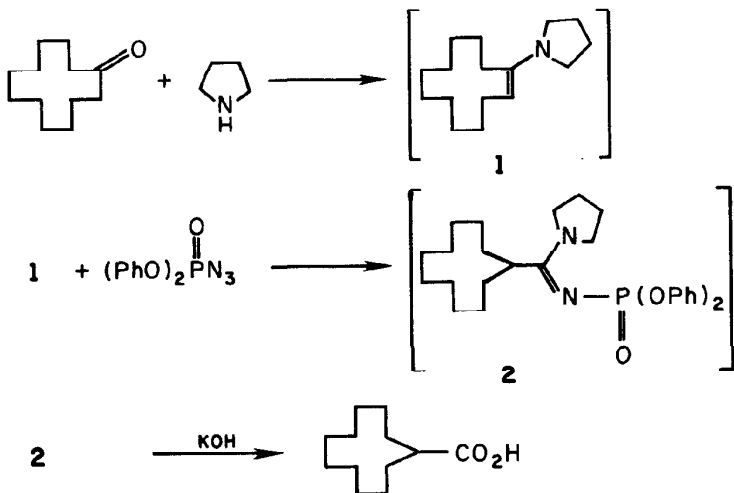
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diphenyl phosphorazidate: Phosphorazidic acid, diphenyl ester (8,9);
(26386-88-9)

Diphenyl phosphorochloridate; Diphenyl chlorophosphate: Phosphorochloridic
acid, diphenyl ester (8,9); (2524-64-3)

Sodium azide (8,9); (26628-22-8)

CYCLOUNDECANECARBOXYLIC ACID



Submitted by Yasumasa Hamada and Takayuki Shioiri¹.

Checked by M. F. Semmelhack and E. Spiess.

1. Procedure

To a 300-mL, round-bottomed flask fitted with a water separator, (Note 1) which contains 15 g of Linde 4Å molecular sieve 1/16-inch pellets and is filled with toluene, are added 7.3 g (0.04 mol) of cyclododecanone, 11.4 g (0.16 mol) of pyrrolidine, 100 mL of toluene, and 0.57 g (0.004 mol) of boron trifluoride etherate. The solution is heated under reflux for 20 hr. The water separator is replaced by a distillation head, and about 90 mL of the toluene is removed by distillation at atmospheric pressure. The residue containing 1-(N-pyrrolidino)-1-cyclododecene (1) is used in the next step without further purification (Note 2).

The crude enamine (1) is dissolved in 20 mL of toluene, and the solution is transferred (Note 3) to a 100-mL, three-necked flask equipped with a magnetic stirring bar, 50-mL dropping funnel, reflux condenser protected with a calcium chloride tube, and a thermometer immersed in the solution. A solution of 13.2 g (0.048 mol) of diphenyl phosphorazidate (Note 4; *WARNING*) in 20 mL of toluene is added with stirring during 30 min while the reaction temperature is maintained at about 25°C. The mixture is stirred for 4 hr at 25°C and heated at reflux for 1 hr. The mixture is transferred to a 300-mL, round-bottomed flask and most of the toluene is removed under reduced pressure to yield 23.7 g of a reddish-brown oil, 2 (Note 5).

Ethylene glycol (200 mL) and 40 g (0.71 mol) of potassium hydroxide are added to the residual oil. The mixture is heated at reflux for 24 hr, and then concentrated at 80-115°C (25 mm) (bath temperature is about 190°C) until 100 mL of the distillate is collected. The residue is dissolved in 300 mL of water, and cooled to room temperature. Carbon dioxide is introduced as a gas

until the pH of the solution reaches 9. The mixture is washed with three 80-mL portions of diethyl ether (Note 6). The aqueous layer is acidified with about 53 mL of concentrated hydrochloric acid, and extracted with four 80-mL portions of benzene. The combined benzene extracts are washed with 50 mL of water and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give 4.5-5.5 g of a black-brown oil. Distillation of the oil at 110-115°C (0.1 mm) yields 3.5-3.8 g (40-48%) of cycloundecanecarboxylic acid as a colorless oil.

2. Notes

1. The apparatus described in *Organic Syntheses*² is satisfactory.
2. Pure 1-(N-pyrrolidino)-1-cyclododecene, bp 144°C (1.5 mm), may be isolated by distillation through a Vigreux column.
3. The original flask used for the enamine formation can be used after the attachment of a Y-shape tube fitted with a dropping funnel and a reflux condenser protected with a tube packed with a drying agent such as anhydrous calcium chloride.
4. Diphenyl phosphorazidate is prepared by the action of sodium azide with diphenyl phosphorochloridate (preceding procedure, this volume).³ It is also available from Aldrich Chemical Co. and was used after purification by distillation at 134-136°C (0.2 mm). **WARNING:** Diphenyl phosphorazidate may produce explosive hydrogen azide when it is in contact with moisture for a long time. When diphenyl phosphorazidate, which has been stored for a long time, is used, it should be washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate before distillation.

5. Purification of 1 g of the crude oil was made by column chromatography using 50 g of Merck silica gel with 0.063-0.200-mm particles (catalog No. 1134) in a column 2.2- x 40-cm and 1:1 (V/V) ethyl acetate-hexane as eluant to give pure diphenyl (cycloundecyl-1-pyrrolidinylmethylene)phosphoramidate (2) as a colorless oil, 632 mg (78%). When a Merck precoated silica gel F254 thin layer plate, layer thickness 0.25 mm, is developed with 1:1 (V/V) ethyl acetate-hexane and visualized with ultraviolet light, the phosphoramidate appears at R_f 0.3. Thus the crude oil contained about 15 g of the phosphoramidate.

6. This procedure is designed primarily to remove phenol.

3. Discussion

Cycloundecanecarboxylic acid has been prepared by the bromination of cyclododecanone followed by the Favorskii rearrangement of 2-bromocyclododecanone.⁴

The present preparation illustrates a general and convenient method for ring contraction of cyclic ketones.⁵ The first step is the usual procedure for the preparation of enamines. The second step involves 1,3-dipolar cycloaddition of diphenyl phosphorazidate to an enamine followed by ring contraction with evolution of nitrogen. Ethyl acetate and tetrahydrofuran can be used as a solvent in place of toluene. Pyrrolidine enamines from various cyclic ketones smoothly undergo the reaction under similar reaction conditions. Diphenyl (cycloalkyl-1-pyrrolidinylmethylene)phosphoramidates with 5,6,7, and 15 members in the ring have been prepared in yields of 68-76%.

The third step is hydrolysis of the N-phosphorylated amidines which is carried out by either acid or alkali depending on the substrate.

Similar reaction sequences can be used successfully to convert alkyl aryl ketones to α -arylkanoic acids.⁶

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diphenyl phosphorazidate: Phosphorazidic acid, diphenyl ester (8,9);
(26386-88-9)

Cycloundecanecarboxylic acid (8,9); (4373-07-3)

Cyclododecanone (8,9); (830-13-7)

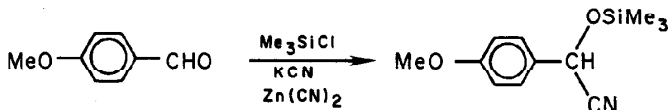
Pyrrolidine (8,9); (123-75-1)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃)
(1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9);
(109-63-7)

IN SITU CYANOSILYLATION OF CARBONYL COMPOUNDS:

O-TRIMETHYLSILYL-4-METHOXYMANDELONITRILE

(Benzeneacetoneitrile, 4-methoxy- α -[(trimethylsilyl)oxy]-)



Submitted by J. K. Rasmussen and S. M. Heilmann¹.

Checked by M. F. Semmelhack and Raj N. Misra.

1. Procedure

Caution! Potassium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a nitrogen-inlet tube, and a rubber septum (Note 1) are placed 97.5 g (1.5 mol) of finely ground potassium cyanide (Note 2), 81.4 g (0.75 mol, 95.2 mL) of chlorotrimethylsilane (Note 3), 68 g (0.5 mol) of p-anisaldehyde (Note 4), 100 mL of dry acetonitrile (Note 5) and 0.5 g (4.25 mmol) of zinc cyanide (Note 6). The reaction mixture is blanketed with dry nitrogen (Note 7), stirring is begun, and the temperature is raised (heating mantle) to maintain gentle reflux. Heating is continued under these conditions for 30 hr (Note 8), with the occasional removal of small samples by

syringe for monitoring by GLC (Note 9). Upon completion of the reaction, the mixture is cooled to ambient temperature and filtered. The filter cake is washed twice with 50 mL of dry acetonitrile and the combined filtrates are concentrated on a rotary evaporator. The residue is distilled at reduced pressure (Note 10). The yield of the colorless liquid (Note 10), which boils at 93-98°C (0.15 mm), amounts to 105-115 g (90-98% based on p-anisaldehyde).

2. Notes

1. All glassware was oven-dried overnight at 130°C, assembled hot, and allowed to cool under a flow of dry nitrogen.

2. Reagent grade potassium cyanide was purchased from Matheson, Coleman and Bell, and dried at 115°C (0.5 mm) for 24 hr. The checkers found it necessary to use newly purchased potassium cyanide. The use of potassium cyanide which was several years old gave incomplete reaction even at extended reaction times. The large excess of potassium cyanide is used simply to obtain convenient reaction times. For comparison, use of 1.5 equiv of KCN gave 38% conversion under conditions where 3 equiv produced 100% conversion.

3. Chlorotrimethylsilane was supplied by Petrarch Systems, Inc., and used without further purification.

4. p-Anisaldehyde, 95%, (4-methoxybenzaldehyde) was used as supplied by Aldrich Chemical Co.

5. Acetonitrile, 99%, supplied by Aldrich Chemical Co., was dried over Linde type 4Å molecular sieves for 12 hr and decanted.

6. Technical grade zinc cyanide was used as supplied by Matheson, Coleman and Bell. Other Lewis acids, notably aluminum chloride, zinc bromide, and zinc iodide may be used as catalysts for the reaction.

7. To "blanket with nitrogen," the checkers simply prepared the reaction mixture with the flask open, introduced a flow of nitrogen over the surface for a few minutes, and then closed the system with an exit through a mercury bubbler to maintain a positive pressure.

8. The reaction time required depends on the catalyst. Zinc iodide, zinc cyanide, and zinc bromide produce essentially complete conversion under these conditions in approximately 16.5, 28 and 30 hr, respectively, probably reflecting solubility differences. When zinc iodide is used, the distilled product is often colored because of the formation of small amounts of iodine.

9. This may be done using a simple boiling point column. We have employed either 10% UCW-98 on Chromosorb W or SP-2100 on 80/100 Supelcoport G2642. The checkers did not monitor the reaction except to extract a small sample after 30 hr in order to verify the absence of starting aldehyde by ^1H NMR spectroscopy.

10. Distillation should be below 100°C . In some instances, at distillation temperatures in excess of 100°C , reversion to the starting aldehyde and trimethylsilyl cyanide has been observed. The pure compound shows the following spectral data: ^1H NMR (CCl_4): δ 0.28 (s, 9 H), 3.86 (s, 3 H), 5.35 (s, 1 H), 6.83 (d, $J = 9$, 2 H), 7.35 (d, $J = 9$, 2 H); IR (film) cm^{-1} : 2965, 1614, 1512, 1258, 1180, 1089, 878, 850. The purity of the crude product is generally such that a distillation forecut need not be taken.

3. Discussion

Cyanosilylations have generally been accomplished by addition of a trialkylsilyl cyanide to the corresponding aldehyde or ketone.²⁻⁵ Although this method is straightforward and proceeds in good to excellent yield, use of pre-

formed trialkylsilyl cyanides has a number of disadvantages, particularly when one considers larger scale preparations. Trialkylsilyl cyanides can be prepared⁶ by treatment of the corresponding silyl chlorides either with silver cyanide or with lithium cyanide generated in situ by reaction of lithium hydride with hydrogen cyanide. The former procedure involves the use of stoichiometric quantities of a rather expensive reagent, while the latter involves handling fairly large quantities of hydrogen cyanide gas. In addition, both procedures require relatively long reaction times, distillation of the silyl cyanide, and produce only moderate to good yields. More recently, improved syntheses of trimethylsilyl cyanide have appeared.^{7,8} Commercially available trimethylsilyl cyanide is also rather expensive.

Silylated cyanohydrins have also been prepared via silylation of cyanohydrins themselves⁹ and by the addition of hydrogen cyanide to silyl enol ethers.¹⁰ Silylated cyanohydrins have proved to be quite useful in a variety of synthetic transformations, including the regiospecific protection of p-quinones,¹¹ as intermediates in an efficient synthesis of α -aminomethyl alcohols,⁶ and for the preparation of ketone cyanohydrins themselves.¹² The silylated cyanohydrins of heteroaromatic aldehydes have found extensive use as acyl anion equivalents, providing general syntheses of ketones¹³ and acylolins.¹⁴

The in situ cyanosilylation of p-anisaldehyde is only one example of the reaction which can be applied to aldehydes and ketones in general.¹⁵ The simplicity of this one-pot procedure coupled with the use of inexpensive reagents are important advantages over previous methods. The silylated cyanohydrins shown in the Table were prepared under conditions similar to those described here. Enolizable ketones and aldehydes have a tendency to produce silyl enol ethers as by-products in addition to the desired cyanohydrins. The

problem can be overcome by using a modified procedure in which dimethylformamide is employed as solvent.¹⁵

TABLE
In Situ CYANOSILYLATION OF CARBONYL COMPOUNDS

$\begin{array}{c} \text{OSi(CH}_3\text{)}_3 \\ \\ \text{R}^1\text{-C-R}^2 \\ \\ \text{CN} \end{array}$	Distilled Yield (%)	Bp. (°C) (pressure, mm)
$\text{R}^1=\text{C}_6\text{H}_5$, $\text{R}^2=\text{H}$	95-98	93-95 (1.75)
$\text{R}^1=4\text{-CH}_3\text{C}_6\text{H}_4$, $\text{R}^2=\text{H}$	91	87 (0.45)
$\text{R}^1=2\text{-ClC}_6\text{H}_4$, $\text{R}^2=\text{H}$	99	92-93 (0.45)
$\text{R}^1=4\text{-ClC}_6\text{H}_4$, $\text{R}^2=\text{H}$	93	100 (0.45)
$\text{R}^1=\text{C}_6\text{H}_5$, $\text{R}^2=\text{CH}_3$	93	73-75 (0.9)
$\text{R}^1, \text{R}^2=(\text{CH}_2)_5$	89	96 (15)
$\text{R}^1=n\text{-C}_6\text{H}_{11}$, $\text{R}^2=\text{H}$	87	106-108 (6.5)

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

O-Trimethylsilyl-4-methoxymandelonitrile: Benzeneacetonitrile, 4-methoxy- α -
[(trimethylsilyl)oxy]- (10); (66985-48-6)

Potassium cyanide (8,9); (151-50-8)

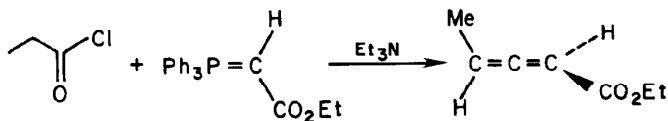
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

p-Anisaldehyde (8); Benzaldehyde, 4-methoxy- (9); (123-11-5)

Zinc cyanide (8,9); (557-21-1)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl- (8,9); (7677-24-9)

**α -ALLENIC ESTERS FROM α -PHOSPHORANYLIDENE ESTERS
AND ACID CHLORIDES: ETHYL 2,3-PENTADIENOATE
(2,3-Pentadienoic acid, ethyl ester)**



Submitted by Robert W. Lany^{1a} and Hans-Jürgen Hansen^{1b}.

Checked by William F. Burgoyne and Robert M. Coates.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a nitrogen inlet, a 250-mL, pressure-equalizing dropping funnel fitted with a gas outlet, and a Teflon-coated magnetic stirring bar. The flask is charged with 300 mL of dichloromethane (Note 1) and 34.8 g (0.10 mol) of ethyl (triphenylphosphoranylidene)acetate (Note 2) and flushed with nitrogen. The yellow solution is stirred at 25°C as a solution of 10.1 g (0.10 mol) of triethylamine (Note 3) in 100 mL of dichloromethane is added dropwise over 5 min. After 10 min, 9.25 g (0.10 mol) of propionyl chloride (Note 4) in 100 mL of dichloromethane is added dropwise to the vigorously stirred solution over 15 min (Note 5). Stirring is continued for an additional 0.5 hr (Note 6) after which the clear, yellow-tinted mixture is evaporated on a rotary evaporator at reduced pressure

using a water bath maintained at 25°C (Note 7). A 500-mL portion of pentane (Note 8) is added to the semi-solid residue, and the slurry is allowed to stand for 2 hr while it is shaken periodically to facilitate solidification and to complete the extraction of the product. The precipitate is removed by filtration through a coarse, sintered-glass Buchner funnel, and the filter cake is washed with a 50-mL portion of pentane. The filtrates are combined and concentrated at reduced pressure to approximately one-fourth of the original volume using a water bath maintained at 25°C. The mixture is filtered again to remove triphenylphosphine oxide, and the remaining solvent is then evaporated. Rapid distillation of the residual liquid in a short-path distillation apparatus under reduced pressure (Note 9) affords a small forerun amounting to 0.5 mL or less and 7.8-8.1 g (62-64%) of ethyl 2,3-pentadienoate, bp 57-59°C (12-14 mm) (Notes 10 and 11).

2. Notes

1. Dichloromethane was purified by percolation through Woelm activity grade 1 basic alumina and stored under nitrogen.

2. Ethyl (triphenylphosphoranylidene)acetate is available from Fluka AG and Tridom Chemical Inc. under the name (ethoxycarbonylmethylene)triphenylphosphorane and from Aldrich Chemical Company, Inc. under the name (carbethoxymethylene)triphenylphosphorane. The reagent may be prepared from triphenylphosphine and ethyl bromoacetate by the following procedure.²

A 1-L, two-necked, round-bottomed flask fitted with a dropping funnel and a mechanical stirrer is charged with 131.0 g (0.5 mol) of triphenylphosphine (Fluka AG, purum) and 250 mL of benzene (Merck, pro analysi). The solution is stirred vigorously while 83.5 g (0.5 mol) of ethyl bromoacetate (Fluka AG,

practical grade) is added dropwise at a rate that maintains the reaction mixture at, or slightly above, room temperature. After a total of 2 hr the reaction is complete and the colorless phosphonium salt is filtered. The salt is washed with 300 mL of cold benzene and 200 mL of pentane and then dissolved in 3 L of water at room temperature. Some further organic impurities are removed by extraction with ether after which 2 drops of 2% alcoholic phenolphthalein are added. The aqueous solution is stirred vigorously and cooled in an ice bath as 2 M aqueous sodium hydroxide is added slowly until the pink endpoint is reached (pH 8-10). The crystalline phosphorane is collected by filtration, washed thoroughly with cold water, and dried, first with a rotary evaporator under reduced pressure at 60°C and then overnight in a drying oven at 180 mm and 70°C. The white to cream-colored crop of ethyl (triphenylphosphoranylidene)acetate, mp 124-126°C, weighs 150-156 g (86-90%) and may be used for the preparation of α -allenic esters without further purification.

3. Triethylamine was supplied by Fluka AG and Aldrich Chemical Company, Inc.

4. Propionyl chloride was purchased from Fluka AG and Aldrich Chemical Company, Inc. and was freshly distilled at 78-80°C (760 mm) prior to use.

5. The checkers maintained the temperature of the reaction mixture at ca. 25°C by cooling with a water bath during the addition of propionyl chloride.

6. The progress of the reaction may be followed by analytical thin-layer chromatography on alumina. The submitters used polygram pre-coated plastic sheets (Alox N/UV₂₅₄) purchased from Macherey-Nagel, Inc. The plates were developed with 1:1 hexane-ether and stained with basic permanganate. The R_f of the product is 0.56.

7. For the isolation of relatively volatile α -allenic esters such as ethyl 2,3-pentadienoate, the submitters recommend that the rotary evaporation be carried out with cooling in an ice bath. When this precaution was taken, the submitters obtained 8.5-9.5 g (67-75%) of product after distillation.

8. The checkers dried the pentane over sodium wire prior to use.

9. The checkers stirred the distilling liquid rapidly with a magnetic stirrer and maintained a bath temperature of 75-85°C throughout the distillation.

10. Ethyl 2,3-pentadienoate has the following spectral properties: IR (thin film) cm^{-1} : 1965, 1720, 1410, 1250, 1025, 865, 790; ^1H NMR (CCl_4) δ : 1.26 (t, 3 H, $J = 7$, OCH_2CH_3), 1.78 (m, 3 H, CH_3), 4.11 (q, 2 H, $J = 7$, OCH_2CH_3), 5.28-5.68 (m, 2 H, at C-2 and C-4).

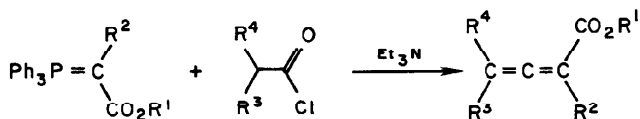
11. On 0.01-mol scale the yield of ethyl 2,3-pentadienoate is 0.79-0.93 g (64-74%). The product was purified by bulb-to-bulb distillation with a Kugelrohr apparatus at 12-14 mm with an oven temperature at 75-85°C.

3. Discussion

The acylation of Wittig reagents provides the most convenient means for the preparation of allenes substituted with various electron-withdrawing substituents.³ The preparation of α -allenic esters has been accomplished by the reaction of resonance-stabilized phosphoranes with isolable ketenes⁴⁻⁹ and ketene itself¹⁰ and with acid chlorides in the presence of a second equivalent of the phosphorane.⁵ The disadvantages of the first method are the necessity of preparing the ketene and the fact that the highly reactive mono-substituted ketenes evidently cannot be used. The second method fails when the α -carbon of the phosphorane is unsubstituted.¹¹

The present procedure affords a general method for preparing α -allenic esters (Table I) which avoids the limitations of the previous methods.¹² Thus, α -allenic esters unsubstituted at C-2 are now available in generally satisfactory yields. Ethyl 2,3-pentadienoate, the title compound, had not been prepared prior to the development of this procedure by the submitters. The mild conditions, (i.e., room temperature for relatively short times), avoid the base-catalyzed isomerization of the conjugated allenes to acetylenes.¹³ The corresponding phosphonium salts may also be used directly in the reaction provided two equivalents of triethylamine are employed, obviating the lengthy process for drying the phosphorane.¹⁴ Dichloromethane and acetonitrile have been used as solvents for the reaction.¹² The α -allenic esters are usually obtained in analytically pure form after bulb-to-bulb distillation. They may also be purified by column chromatography on alumina with 9:1 hexane-ether as eluant.¹⁴

TABLE I
PREPARATION OF α -ALLENIC ESTERS BY THE WITTIG-REACTION¹²



R ¹	R ²	R ³	R ⁴	Solvent	Procedure ^a	Yield(%)
CH ₃	H	H	H	CH ₂ Cl ₂	A	40
C ₂ H ₅	H	(CH ₃) ₃ C	H	CH ₃ CN	B	55
CH ₃	H	C ₆ H ₅	H	CH ₃ CN	B	23
C ₂ H ₅	CH ₃	H	H	CH ₂ Cl ₂	A	59
C ₂ H ₅	CH ₃	CH ₃	H	CH ₂ Cl ₂	A	74
C ₂ H ₅	CH ₃	CH ₃	CH ₃	CH ₂ Cl ₂	B	39
CH ₃	CH ₃	(CH ₃) ₃ C	H	CH ₃ CN	B	66
C ₂ H ₅	CH ₃	C ₆ H ₅	H	CH ₂ Cl ₂	A	70

^aThe reaction times varied from 10 min to 18 hr. A=the corresponding phosphonium salt was used with the addition of two moles of triethylamine. B=the corresponding phosphorane was used with the addition of one mole of triethylamine.

The submitters have shown that these reactions proceed by dehydrochlorination of the acid chloride to the ketene, which is then trapped by reaction with the phosphorane. The resulting betaine decomposes to the allenic ester via an oxaphosphetane. In contrast, the reaction of acid chlorides with 2 equivalents of phosphoranes involves initial acylation of the phosphorane followed by proton elimination from the phosphonium salt.⁵

1. (a) Zentrale Forschungslaboratorien, CIBA-Geigy AG, Postfach CH-4002, Basel, Switzerland. (b) Zentrale Forschungseinheiten, F. Hoffmann-La Roche & Co. AG, Postfach, CH-4002 Basel, Switzerland. Work done at the Institute of Organic Chemistry, University of Fribourg, CH-1700 Fribourg, Pérolles, and supported by the Swiss National Science Foundation.
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Appendix

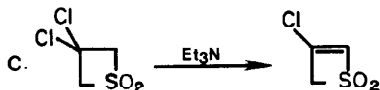
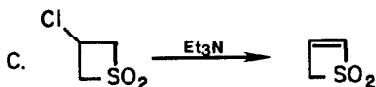
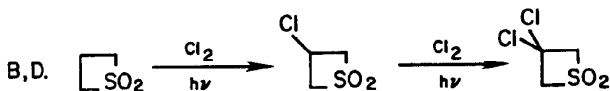
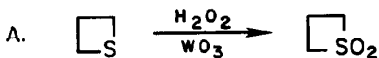
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(Carbethoxymethylene)triphenylphosphorane, (Ethoxycarbonylmethylene)triphenylphosphorane: Acetic acid, (triphenylphosphoranylidene)-, ethyl ester (8,9); (1099-45-2)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

THIETE 1,1-DIOXIDE AND 3-CHLOROTHIETE 1,1-DIOXIDE
(2H-Thiete 1,1-dioxide and 2H-thiete, 3-chloro- 1,1-dioxide)



Submitted by Thomas C. Sedergran and Donald C. Dittmer¹.

Checked by M. F. Semmelhack, Elena M. Bingham, William A. Sheppard,
and Joseph J. Bozell.

1. Procedure

A. *Thietane 1,1-dioxide*. The pH of a solution of tungstic acid ($\text{WO}_3 \cdot \text{H}_2\text{O}$) (1.1 g, 0.044 mol) (Note 1) in 280 mL of distilled water is adjusted to 11.5 by addition of 10% aqueous sodium hydroxide; the white suspension of the tungstate catalyst is added to a 1-L, round-bottomed flask fitted with a mechanical stirrer and a pressure-equalizing addition funnel. The tungstic acid-water mixture is cooled to 0–10°C by means of an ice-salt bath; glacial acetic acid (50 mL) and trimethylene sulfide (thietane) (47.5 g, 0.641 mol, d 1.028) (Note 2) are added. The chilled mixture is stirred, and 30% hydrogen peroxide (189 mL) is added carefully by means of the addition funnel over a period of 2 hr (Note 3). The mixture is stirred at 0–10°C for an additional hour, transferred to an evaporating dish and heated to near dryness on a steam bath. The resulting solid material is triturated five times with 100-mL portions of hot chloroform, any catalyst being removed by filtration. The chloroform solutions are combined, dried over anhydrous magnesium sulfate and the solvent removed via a rotary evaporator to give a white solid (60.3–63.7 g, 0.57–0.60 mol, 88.7–93.7%), mp 74–76°C (lit² mp 75.5–76°C).

B. *3-Chlorothietane 1,1-dioxide*. Thietane 1,1-dioxide (14.0 g, 0.132 mol) is placed in a three-necked, 500-mL, round-bottomed flask fitted with a magnetic stirrer, reflux condenser and a chlorine bubbler. (*Caution! Since chlorine is poisonous, the reaction involving it should be done in a good hood.*) Carbon tetrachloride (300 mL) is added to the flask (Note 4) and the suspension is irradiated by a 250-watt sunlamp positioned as close as possible to the reaction flask without touching it (Note 5) while chlorine is bubbled through the solution for 15 min at a moderate rate (Note 6). A copious white precipitate forms and irradiation and addition of chlorine must be stopped at

this point (or 10 min after the first appearance of a precipitate) to avoid dichlorination. The reaction mixture is cooled to room temperature and filtered to give a white, fluffy product (5.4-8.1 g, 30-44%) which is crystallized from chloroform, mp 136-137°C (lit³ mp 136.5-137.5°C).

C. *Thiete 1,1-dioxide*. A sample of 3-chlorothietane 1,1-dioxide (8.0 g, 0.057 mol) is dissolved in dry toluene (300 mL) (Note 7) in a 500-mL, two-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, heating mantle (or silicone oil bath), and thermometer. The reaction is heated to 60°C and triethylamine (28.7 g, 0.28 mol, 39.5 mL) is added through the condenser. The reaction mixture is stirred for 4 hr and triethylamine hydrochloride is removed by filtration and washed with toluene (100 mL). Toluene is removed on a rotary evaporator and the residue is recrystallized from diethyl ether-ethanol (Note 8) to give a white solid (4.5-4.8 g, 75-81%); mp 49-50°C (lit³ mp 52-54°C).

D. *3,3-Dichlorothietane 1,1-dioxide*. Thietane 1,1-dioxide (5.0 g, 0.047 mol) is placed in a 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and chlorine gas bubbler. Carbon tetrachloride (350 mL) is added and the solution is irradiated with a 250-watt sunlamp (Note 5) while chlorine is bubbled through the stirred mixture for 1 hr (Note 9). Irradiation and chlorine addition are stopped and the reaction mixture is allowed to cool to room temperature. The product is collected by filtration as a white solid (4.0-4.4 g, 49-53%), mp 156-158°C (Note 10). The product can be used without further purification or it can be recrystallized from chloroform.

E. *3-Chlorothiete 1,1-dioxide*. A solution of 3,3-dichlorothietane 1,1-dioxide (4.0 g, 0.023 mol) in toluene (150 mL) is placed in a 250-mL, round-bottomed, two-necked flask equipped with a heating mantle (or silicone oil

bath), magnetic stirrer, reflux condenser, and thermometer. The solution is heated to 60°C and triethylamine (2.54 g, 0.025 mol, 3.5 mL) is added dropwise through the condenser over a 10-min period. The solution is stirred for 2 hr at 60°C and cooled to room temperature. The triethylamine hydrochloride is collected by filtration and washed with hot toluene (50 mL). Removal of toluene on a rotary evaporator gives a white solid (2.7-3.0 g, 84-93%) which is recrystallized from chloroform-hexane, mp 118-120° (Note 11).

2. Notes

1. The tungstic acid was used as supplied by the Eastman Kodak Company.
2. The trimethylene sulfide was used as supplied by the Aldrich Chemical Company.
3. The addition rate of the hydrogen peroxide must be adjusted so that the temperature of the reaction mixture does not rise above 10°C. The yield is reduced if the temperature is allowed to rise above that point. The end point of the reaction, when excess peroxide is present, can be determined with potassium iodide - starch test paper. The yield also is reduced if more than a slight excess of hydrogen peroxide is used.
4. The sulfone is not completely dissolved at this point. The prescribed ratio of sulfone to carbon tetrachloride (0.0467 g mL) is important. If it is less (i.e., more carbon tetrachloride relative to sulfone), considerable 3,3-dichlorothietane 1,1-dioxide will be formed.
5. Any commercial sunlamp is satisfactory and should be used with eye protection. Carbon tetrachloride boils gently because of the heat from the lamp.

6. The submitters suggested adding the chlorine at such a rate that a constant yellow color is maintained in the solution or suspension. The checkers found that, depending on the rate of chlorine introduction, it took from 10 to 35 min for the appearance of the white precipitate. In each run, the monochlorinated product was contaminated with a small amount (5-10% by NMR integration) of either starting material or dichlorinated product. The checkers found that the optimum yield of monochlorinated product was obtained when the chlorine was bubbled into the solution through a 1/4" glass tube at a rate estimated to be between 5-15 bubbles per sec. The suspended sulfone dissolves as the reaction proceeds.

7. Toluene was dried over 4Å molecular sieves. Benzene may be used also.

8. The product is heated in about 25-30 mL of diethyl ether, and ethanol is added dropwise until a solution is obtained. The checkers found that the thiete could also be crystallized by gently heating the crude material in diethyl ether (~100 mL) until it dissolves, followed by cooling to -15°C.

9. If the reaction time is less than 1 hr, a mixture of monochloro- and dichlorosulfone is obtained.

10. The spectral properties of the product are as follows: IR (KBr disc) cm^{-1} : 2950 (m), 1370 (m, SO_2), 1310 (m), 1210 (m), 1140 (m, SO_2), 970 (m), 940 (m), 820 (w); ^1H NMR (chloroform- d) δ : 5.0 (s, 4 H, $\text{CH}_2\text{SO}_2\text{CH}_2$). Anal. Calcd. for $\text{C}_3\text{H}_4\text{Cl}_2\text{O}_2\text{S}$: C, 20.70; H, 2.30. Found: C, 20.81; H, 2.39.

11. The spectral properties of the product are as follows: IR (KBr disc) cm^{-1} : 1540 (m, $>\text{C}=\text{C}<$), 1400 (w), 1300 (s, SO_2), 1210 (s), 1140 (s, SO_2), 1020 (m), 770 (m); ^1H NMR (chloroform- d) δ : 6.8 (s, 1 H, $\text{CH}=\text{C}$), 4.6 (s, 2 H, CH_2-SO_2). Anal. Calcd. for $\text{C}_3\text{H}_3\text{ClO}_2\text{S}$: C, 26.00; H, 2.17. Found: C, 25.78; H, 2.02.

3. Discussion

This preparation of thiete 1,1-dioxide is more direct and less tedious than previous methods.^{3,4,5}

Oxidation of trimethylene sulfide catalyzed by tungstic acid⁶ is preferred to the uncatalyzed reaction: Yields are better and the reaction time is shortened by elimination of an induction period.

Selective chlorination of the 3-position of thietane 1,1-dioxide may be a consequence of hydrogen atom abstraction by a chlorine atom. Such reactions of chlorine atoms are believed to be influenced by polar effects, preferential hydrogen abstraction occurring remotely from an electron withdrawing group.⁷ The free radical chain reaction may be propagated by attack of the 3-thietanyl 1,1-dioxide radical on molecular chlorine.

Conversion of 3-chlorothietane 1,1-dioxide to the 3-(N,N-dimethylamino) derivative followed by reduction, quaternization, and Hofmann elimination affords a convenient route to the highly reactive thiete (thiacyclobutene).^{4,8}

The following compounds have been obtained from thiete 1,1-dioxide: Substituted cycloheptatrienes,⁹ benzyl α -toluenethiosulfinate,¹⁰ pyrazoles,¹¹ naphthothiete 1,1-dioxides,¹² and 3-substituted thietane 1,1-dioxides.¹³ It is a dienophile in Diels-Alder reactions^{9,12,14} and undergoes cycloadditions with enamines, dienamines, and ynamines.¹⁵ Thiete 1,1-dioxide is a source of the novel intermediate, vinylsulfene ($\text{CH}_2=\text{CHCH}=\text{SO}_2$), which undergoes cycloadditions to strained olefinic double bonds,¹⁶ reacts with phenol to give allyl sulfonate derivatives¹⁷ or cyclizes unimolecularly to give an unsaturated sultene.¹⁷ Platinum¹⁸ and iron¹⁹ complexes of thiete 1,1-dioxide have been reported.

3-Chlorothiете 1,1-dioxide is a potentially useful intermediate for the preparation of other 3-substituted thiете 1,1-dioxides via addition-elimination reactions.

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Appendix

**Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)**

Thiete 1,1-dioxide: 2H-Thiete 1,1-dioxide (9); (7285-32-7)

Thietane 1,1-dioxide (9); (5687-92-3)

Tungstic acid (8,9); (7783-03-1)

Trimethylene sulfide (8); Thietane (9); (287 27 4)

3-Chlorothietane 1,1-dioxide: Thietane, 3-chloro- 1,1-dioxide (8,9);
(15953-83-0)

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CONTENTS

Dieter Seebach, Marius A. Sutter, Roland H. Weber, and Max F. Ziger	1	YEAST REDUCTION OF ETHYL ACETOACETATE: (S)-(+)-ETHYL 3-HYDROXYBUTANOATE
J. Bryan Jones and Ignac J. Jakovac	10	PREPARATION OF CHIRAL, NON-RACEMIC γ -LACTONES BY ENZYME-CATALYZED OXIDATION OF MESO-DIOLS: (+)-(1R, 6S)-8-OXABICYCLO [4.3.0]NONAN-7-ONE
I. Ojima, T. Kogure, and Y. Yoda	18	ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE: D-(-)-PANTOYL LACTONE
Zoltan G. Hajos and David R. Parrish	26	(+)-(7aS)-2,3,7,7a-TETRAHYDRO-7a- METHYL-1H-INDENE-1,5-(6H)-DIONE
Paul Buchschacher and A. Fürst	37	ASYMMETRIC SYNTHESIS OF (S)-8a- METHYL-3,4,8,8a-TETRAHYDRO- 1,6(2H,7H)-NAPHTHALENEDIONE
John J. Partridge, Naresh K. Chadha, and Milan R. Uskokovic	44	ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES: SYNTHESIS OF METHYL (1R,5R)-5- HYDROXY-2-CYCLOPENTENE-1-ACETATE
M. Mark Midland and Richard S. Graham	57	ASYMMETRIC REDUCTION OF α,β - ACETYLENIC KETONES WITH B-3- PINANYL-9-BORABICYCLO- [3.3.1]NONANE: (R)-(+)-1-OCTYN-3-OL
J. Gordon Hill, K. Barry Sharpless, Christopher M. Exon, and Ronald Regenye	66	ENANTIOSELECTIVE EPOXIDATION OF ALLYLIC ALCOHOLS: (2S,3S)-3-PROPYLOXIRANEMETHANOL
Steven D. Young, Charles T. Buse, and Clayton H. Heathcock	79	2-METHYL-2-TRIMETHYLSILOXYPENTAN- 3-ONE
B. Bal, C. T. Buse, K. Smith, and Clayton H. Heathcock	89	(2SR,3RS)-2,4-DIMETHYL-3- HYDROXYPENTANOIC ACID
Stephen H. Montgomery, Michael C. Pirrung and Clayton H. Heathcock	99	(2SR,3SR)-2,4-DIMETHYL-3- HYDROXYPENTANOIC ACID
Dieter Seebach, Johannes Aebi, and Daniel Wasmuth	109	DIASTEREOSELECTIVE α -ALKYLATION OF β -HYDROXYCARBOXYLIC ESTERS THROUGH ALKOXIDE ENOLATES: (+)-DIETHYL (2S,3R)-3-ALLYL-2- HYDROXYSUCCINATE FROM (-)-DIETHYL S-MALATE

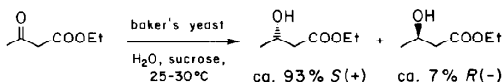
Olivier H. Gringore and Francis P. Rouessac	121	(S)-(+)- γ -BUTYROLACTONE- γ - CARBOXYLIC ACID
Noal Cohen, Bruce L. Banner, Anthony J. Laurenzano, and Louis Carozza	127	2,3-O-ISOPROPYLIDENE-D- ERYTHRONOLACTONE
G. A. Smith and Robert E. Gawley	136	L-VALINOL
Martin K. Ellis and Bernard T. Golding	140	OPTICALLY ACTIVE EPOXIDES FROM VICINAL DIOLS VIA VICINAL ACETOXY BROMIDES: THE ENANTIOMERIC METHYLOXIRANES
J. Salaün and J. Marguerite	147	CYCLOPROPANONE ETHYL HEMIACETAL FROM ETHYL 3-CHLOROPROPANOATE
Michael Van Der Puy and Louis G. Anello	154	HEXAFLUOROACETONE
Oskar Keller, Walter E. Keller, Gert van Look, and Gernot Wersin	160	tert-BUTOXYCARBONYLATION OF AMINO ACIDS AND THEIR DERIVATIVES: N-tert-BUTOXYCARBONYL-L- PHENYLALANINE
William J. Paleveda, Frederick W. Holly, and Daniel F. Veber	171	N-tert-BUTOXYCARBONYL-L- PHENYLALANINE
H. P. Fahrni, U. Lienhard and M. Neuenschwander	175	PEPTIDE SYNTHESIS USING 1-(4- CHLOROPHENYL)-3-(4'-METHYL-1'- PIPERAZINYL)-2-PROPYN-1-ONE AS REAGENT: BENZYLOXYCARBONYL-L- ALANYL-L-CYSTEINE METHYL ESTER AND BENZYLOXYCARBONYL-L-ASPARTYL-(tert- BUTYL ESTER)-L-PHENYLALANYL-L- VALINE METHYL ESTER
B. Neises and Wolfgang Steglich	183	ESTERIFICATION OF CARBOXYLIC ACIDS WITH DICYCLOHEXYLCARBODIIMIDE/4- DIMETHYLAMINOPYRIDINE: tert-BUTYL ETHYL FUMARATE
George A. Olah and Alexander P. Fung	188	HEXAHYDRO-2-(1H)-AZOCINONE
Adolf Thalmann, Konrad Oertle, and Hans Gerlach	192	RICINOLEIC ACID LACTONE
Y. Oikawa, T. Yoshioka, K. Sugano, and Osamu Yonemitsu	198	METHYL PHENYLACETYLACETATE FROM PHENYLACETYL CHLORIDE AND MELDRUM'S ACID

Pierre Crabbé, Bahman Nassim and Maria-Teresa Robert-Lopes	203	ONE-STEP HOMOLOGATION OF ACETYLENES TO ALLENES: PREPARATION OF 4-HYDROXYNONA-1,2-DIENE
T. Shono, Y. Matsumura, and K. Tsubata	206	ANODIC OXIDATION OF N-CARBOMETHOXYPYRROLIDINE: 2-METHOXY-N-CARBOMETHOXYPYRROLIDINE
Andrew D. Batcho and Willy Leimgruber	214	INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH FORMAMIDE ACETALS FOLLOWED BY REDUCTION: 4-BENZYLOXYINDOLE
George W. Parshall	226	HAZARD WARNING: TETRAMETHYL- BIPHOSPHINE DISULFIDE
Unchecked Procedures	227	
Cumulative Author Index for Volumes 60, 61, 62, and 63	231	
Cumulative Subject Index for Volumes 60, 61, 62, and 63	235	

YEAST REDUCTION OF ETHYL ACETOACETATE:

(S)-(+)-ETHYL 3-HYDROXYBUTANOATE

(Butanoic acid, 3-hydroxy-, ethyl ester, (S))



Submitted by Dieter Seebach, Marius A. Sutter, Roland H. Weber,
and Max F. Züger.¹

Checked by Terry Rosen and Clayton H. Heathcock.

1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with mechanical stirrer, bubble counter, and a stopper is charged with 1.6 L tap water, 300 g of sucrose (Note 1), and 200 g baker's yeast (Note 2), which are added with stirring in this order. The mixture is stirred for 1 hr at about 30°C, 20.0 g (0.154 mol) of ethyl acetoacetate (Note 3) are added, and the fermenting suspension (Note 4) is stirred for another 24 hr at room temperature. A warm (ca. 40°C) solution of 200 g sucrose (Note 1) in 1 L of tap water is then added, followed 1 hr later by an additional 20.0 g (0.154 mol) of ethyl acetoacetate (Note 3). Stirring is continued for 50-60 hr at room temperature. When the reaction is complete by gas chromatographic analysis

(Note 5), the mixture is worked up by first adding 80 g of Celite and filtering through a sintered glass funnel (porosity 4, 17 cm diameter). After the filtrate is washed with 200 mL of water, it is saturated with sodium chloride and extracted with five 500-mL portions of ethyl ether (Note 6). The combined ether extracts are dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator at 35°C bath temperature to a volume of 50-80 mL. This residue is fractionally distilled at a pressure of 12 mm through a 10-cm Vigreux column, and the fraction boiling at 71-73°C (12 mm) is collected to give 24-31 g (59-76%) of (S)-(+)-ethyl 3-hydroxybutanoate (Note 7, 8); the specific rotation $[\alpha]_D^{25} + 37.2^\circ$ (chloroform, $n_D^{20} 1.3$) corresponds to an enantiomeric excess of 85% (Note 9).

The enantiomeric excess may be enhanced by several crystallizations of the 3,5-dinitrobenzoate derivative (Note 10).

2. Notes

1. Commercially available sugar (sucrose) from a grocery store is used.

2. Commercially available baker's yeast can be used. The submitters used baker's yeast from E. Klipfel & Co. AG, CH-4310 Rheinfelden (Switzerland). The checkers used Fleischmann's yeast (cubes), obtained from a supermarket, or Red Star Baker's yeast (Universal Food Corporation), obtained from a bakery. The optical rotation of the final product was essentially the same for runs in which the two brands were employed.

3. Ethyl acetoacetate is freshly distilled before use (bp 65°C/12 mm).

4. One to two bubbles per second of CO₂ are developed.

5. A small sample (ca. 1 mL) is removed from the mixture and extracted with ethyl ether. The ether solution is analyzed for remaining ethyl acetoacetate by capillary gas chromatography: 0.3 mm by 20 m glass capillary column Carbowax 20 M, oven temperature 100°C, carrier gas: hydrogen (0.4 atm); retention time of ethyl acetoacetate: 450 sec, of (S)-(+)-ethyl 3-hydroxybutanoate: 610 sec. It is important that all the starting material be consumed. If small amounts of ethyl acetoacetate are detected, 100 g of sucrose is added and the mixture is stirred for a further period of 2 days. The checkers detected the presence of residual ethyl acetoacetate by TLC on 250 micron silica gel plates with 1:1 ether/hexane as eluant. Plates are developed by dipping the dried plate into a solution of 10% vanillin and 5% sulfuric acid in 95% ethanol and then gently warming over a hot plate; ethyl acetoacetate appears as an intense blue spot with R_f 0.45.

6. In the case of emulsions, addition of methanol may be helpful. The very fine and stable emulsion which still remains is included with the aqueous phase.

7. The spectral properties of (S)-(+)-ethyl 3-hydroxybutanoate are as follows: IR^{2a} (film) cm^{-1} : 3440, 2980, 1730, 1375, 1300, 1180, 1030; ¹H NMR^{2b} (CCl_4) δ : 1.15 (d, 3 H, $J = 6.5$, CH_3), 1.28 (t, 3 H, $J = 7$ Hz, CH_3), 2.35 (d, 2 H, $J = 6.5$, CH_2CO), 3.15 (s, 1 H, OH), 4.05 (q, 2 H, $J = 7$, CH_2O), 4.15 (m, 1 H, CHOH).

8. This ester should be stored in a refrigerator as there has been some indication that it may undergo a transesterification/oligomerization upon standing at room temperature.

9. The specific rotation $[\alpha]_D^{25}$ varies from +35.5° to +38° (82-87% enantiomeric excess). The enantiomeric purity can also be checked by formation of the ester with (R)-(+)-1-methoxy-1-trifluoromethylphenylacetyl

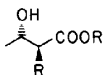
(MTPA) chloride.³ The ^{19}F NMR chemical shifts of the diastereomeric esters are 6.13 (R,R) and 6.01 (R,S) ppm downfield of external trifluoroacetic acid.

10. The procedure of enriching the (S)-(+)-enantiomer to 100% enantiomeric excess by the previously described crystallization method is tedious.⁴ It provides optically pure ethyl (S)-(+)-3-(3',5'-dinitrobenzoyloxy)butanoate of $[\alpha]_{\text{D}}^{25} +26.3^\circ$ (chloroform, c 2), which after cleavage gives enantiomerically pure (S)-(+)-ethyl 3-hydroxybutanoate of $[\alpha]_{\text{D}}^{25} +43.5^\circ$ (chloroform, c 1.0). This optically pure compound has recently become commercially available from Fluka AG, CH-9470 Buchs (Switzerland), but it is very expensive. After submission and checking of this procedure, it was shown⁵ that the ee of the product can be increased to >95% by working under aerobic conditions and by adding the ketoester more slowly.

3. Discussion

3-Hydroxybutanoic acid in both enantiomeric forms has been obtained by resolution of the racemic mixture.⁶ Hydrogenation of methyl acetoacetate using a Raney nickel catalyst which had been treated with tartaric acid resulted in methyl 3-hydroxybutanoate with an enantiomeric excess of 83-88%.⁷ Furthermore, optically active 3-hydroxybutanoic acid has been obtained in good chemical and optical yield by condensation of chiral α -sulphonyl ester enolates with aldehydes followed by desulfurization.⁸ (R)-(-)-Ethyl 3-hydroxybutanoate in 100% enantiomeric excess resulted from depolymerization of poly-(R)-3-hydroxybutanoate, an intracellular storage product of *Alcaligenes eutrophus* H 16.⁹ The method presented in this paper is easy to perform. The (S)-(+)-ethyl 3-hydroxybutanoate obtained may be enriched to 100% enantiomeric excess by crystallization of its 3,5-dinitrobenzoate derivative, followed by alcoholysis.⁴

Optically active ethyl 3-hydroxybutanoate is a very useful chiral building block for natural product synthesis. Some applications are shown in Table I. Alkylation of doubly deprotonated ethyl 3-hydroxybutanoate gives branched structures of the following type:¹⁰



The yeast reduction is not limited to ethyl acetoacetate. It has been applied to other β -keto esters, α -keto esters, α -keto alcohols, α -keto phosphates and some ketones (Table II). The reductions show a high degree of stereoselectivity. The absolute configuration of the product obtained by reduction of a carbonyl group containing a large group L and a small group S to the alcohol may be determined by application of Prelog's rule.^{11,12}

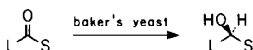
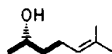
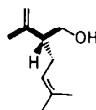
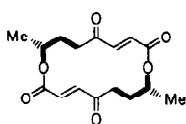
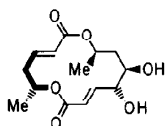
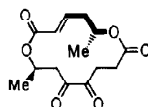
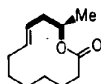
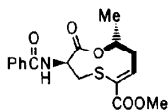
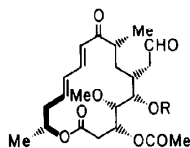


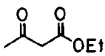
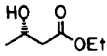
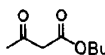
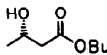
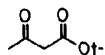
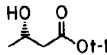
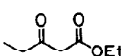
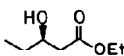
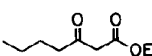
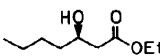
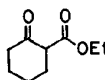
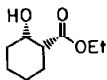
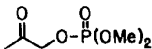
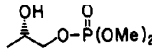
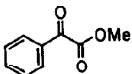
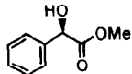
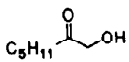
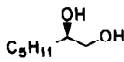
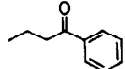
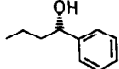
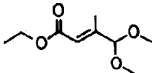
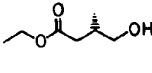
TABLE I

NATURAL PRODUCTS FROM (S)- OR (R)-ETHYL 3-HYDROXYBUTANOATE

The Skeleton of Ethyl 3-Hydroxybutanoate is Indicated by Heavy Lines

(S)-(+)-Sulcatol¹³(R)-(-)-Lavandulol¹⁴(R,R)-Pyrenophorin¹⁵Colletodiol¹⁶(R,R)-(-)-
Grahamimycin A₁¹⁶(R)-(+)-Recifeiolide¹⁷Griseoviridin
precursor¹⁸Carbomycin B¹⁹

Enantioselective preparation of alcohols
from the corresponding ketone by yeast reduction

Substrate	Product	Yield (%)	Enantiomeric excess (%)	Ref.
		57-67	84-87	20
		58	90	9
		61	85	9
		67	40	10a
			>90	10a
		65	86	20b, 21
		57	74	22
		59	>97	20b
		56	100	23
		45	85-87	12
		34	>97	24

1. Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl acetoacetate: Acetoacetic acid, ethyl ester (8); Butanoic acid, 3-oxo-ethyl ester (9); (141-97-9)

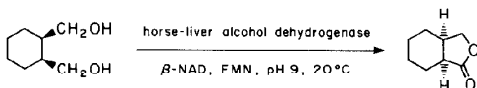
(S)-(+)-Ethyl 3-hydroxybutanoate: Butanoic acid, 3-hydroxy-, ethyl ester, (S)- (9); (56816-01-4)

PREPARATION OF CHIRAL, NON-RACEMIC γ -LACTONES BY ENZYME-

CATALYZED OXIDATION OF MESO-DIOLS:

(+)-(1R, 6S)-8-OXABICYCLO[4.3.0]NONAN-7-ONE

(1(3H)-Isobenzofuranone, hexahydro-, (3aS-cis)-)



Submitted by J. Bryan Jones and Ignac J. Jakovac.¹

Checked by Roland H. Weber, Max F. Züger, and Dieter Seebach.

1. Procedure

In a 1-L Erlenmeyer flask are placed 475 mL of distilled water (Note 1) and 3.75 g (0.05 mol) of reagent grade glycine, and the pH is adjusted to 9 by the careful addition of aqueous 10% sodium hydroxide. In the buffer solution thus obtained are dissolved 2.00 g (13.87 mmol) of cis-1,2-bis(hydroxymethyl)-cyclohexane (Note 2), 0.58 g (0.852 mmol) of β -NAD (Note 3), and 1.8 g (16.2 mmol) of FMN (Note 4). To the clear orange solution obtained is added 80 units of horse liver alcohol dehydrogenase (Note 5). After the solution is gently swirled for 1 min, the pH is readjusted to 9 and the mixture is kept at room temperature (Note 6) with the mouth of the flask loosely covered by a watchglass. After a few minutes the color of the solution begins to darken and after several hours becomes an opaque green-brown. The pH is readjusted

to 9 after 6, 12, 24, 48 and 72 hr by the careful addition of aqueous 10% sodium hydroxide since the pH of the mixture drops progressively as the reaction proceeds. After 4 days (Note 7), the mixture is brought to a pH of ca. 13.3 by the addition of 20 mL of aqueous 50% sodium hydroxide solution. After 1 hr, the mixture is continuously extracted with chloroform for 10 hr (Note 8). The chloroform extract is discarded. The aqueous layer is acidified to pH 3 with concentrated hydrochloric acid and again extracted continuously for 15 hr with chloroform. To the green-orange solution are added charcoal (0.5 g), and magnesium sulfate. The dried and partially decolorized mixture is filtered through a bed of Celite, and the chloroform is removed under reduced pressure using a rotatory evaporator. The residual orange-green oil is distilled in a Kugelrohr to give 1.4-1.5 g (72-77% yield, Note 9) of (+)-(1R, 6S)-8-oxabicyclo[4.3.0]nonan-7-one (> 97% e.e., (Note 10)) as a colorless oil, bp 85-100°C (0.1-0.05 mm), mp 26-29°C, $[\alpha]_D^{22} +51.3^\circ$ (CHCl₃, c 1.1) (Note 11).

2. Notes

1. It is not necessary to use doubly distilled or deionized water in this buffer preparation.

2. cis-1,2-Bis(hydroxymethyl)cyclohexane was purchased from Aldrich Chemical Company, Inc. (or EGA, D-Steinheim).

3. β -NAD is the standard biochemical abbreviation for the coenzyme β -nicotinamide adenine dinucleotide. The β -NAD used was of 95% purity and was purchased from Kyowa Hakko (U.S.A.), New York. It is also available from Sigma Chemical Company.

4. FMN is the standard biochemical abbreviation for flavin mononucleotide (or riboflavin phosphate). The sodium salt (95-97% pure) of FMN is used. This grade is inexpensive and is available from Sigma Chemical Company. Its purpose is to effect recycling² of the catalytic amount used of the much more costly NAD. A larger than stoichiometric amount of FMN is employed in order to ensure rapid recycling of the NAD.

5. Horse liver alcohol dehydrogenase (HLADH or LADH, also called equine liver alcohol dehydrogenase) is the crystalline preparation (> 98% protein) sold by Sigma Chemical Company. It is also available from Worthington and Boehringer. The amount added is quoted in units of activity since the activity of the enzyme from different sources can vary. For example, the Sigma enzyme is sold as having an activity of 1-2 units per mg of protein. The enzyme used in this preparation had 1.5 units of activity per mg. We have used Worthington and Boehringer enzyme with equal success. The activity of the enzyme diminishes slowly on prolonged storage, even at -20°C. For controlled results, the enzyme activity may be determined prior to use and the requisite number of units used.

The assay method of Dalziel³ is convenient. In a recording ultraviolet spectrophotometer set at 340 nm is placed a 3-mL quartz cuvette containing 2.4 mL of 0.10 M glycine-sodium hydroxide buffer solution, pH 9, 500 μ L of a 54 mM solution of ethanol in the same buffer, and 100 μ L of a 15 mM solution of NAD, also in the same pH 9 buffer. The volume is made up to 3.0 mL, and the assay initiated by the addition of 10 μ L of a 1 mg per mL solution of HLADH in 0.10 M "Tris-hydrochloric acid buffer", pH 7.4. The change in optical density at 340 nm is monitored at 25°C and the activity calculated from the following equation:

$$\text{Units of activity/mg protein} = \frac{\Delta OD_{340}/\text{min}}{6.23 \times \text{mg HLADH/mL of assay volume}}$$

If the above assay concentrations are followed exactly, this becomes:

$$\text{Units/mg protein} = \frac{\Delta OD_{340}/\text{min}}{20.75}$$

6. Ambient temperatures of up to 30°C can be employed but the reaction temperature should not be allowed to fall below 20°C.

7. The end of the reaction is checked by gas chromatography using 3% QF-1 or OV-101 on Chromosorb columns. The checkers used an OV-101, at 190°C oven temperature. A sample is extracted with ether. The organic layer is analyzed. At 20°C the reaction usually goes to completion within 4 days.

8. This removes residual starting material and other non-acidic impurities.

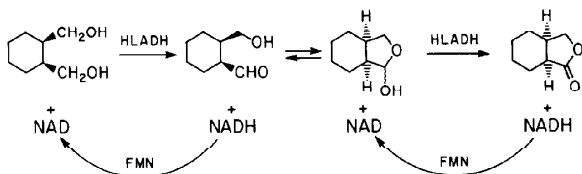
9. Scaling up the preparation is easily accomplished. It is best done by increasing the number of reaction vessels rather than by increasing the reaction volume. For example, 10 g of the cis-diol substrate can be oxidized simultaneously using 2.5 g in each of four 1-L Erlenmeyer flasks as described in the procedure. After 4 days, the reaction mixtures are combined prior to the chloroform extraction and the lactone is isolated.

10. The absolute configuration and optical purity of the lactone was established by its hydrolysis and epimerization to (1R, 2R)-trans-2-hydroxymethylcyclohexanecarboxylic acid followed by lithium aluminum hydride reduction to (1R, 2R)-trans-1,2-bis(hydroxymethyl)cyclohexane.⁴ By ¹H NMR,⁵ the e.e. was > 97%.

11. The spectral properties of the product obtained were as follows: IR (thin film): C = O at 1770 cm^{-1} ; ^1H NMR (CDCl_3) δ : 0.9-2.8 (m, 10 H, all cyclohexane H), 3.87-4.34 (m, 2 H, $\text{CH}_2\text{-O}$),

3. Discussion

Horse liver alcohol dehydrogenase is a well-documented enzyme capable of operating with high stereoselectivity on a broad structural range of alcohol and carbonyl substrates.⁶ The present reaction proceeds via the pathway shown below, where NAD and NADH represent the oxidized and reduced forms, respectively, of the nicotinamide adenine dinucleotide coenzyme.





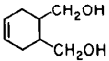

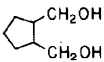

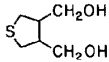



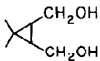

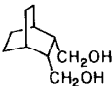

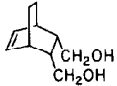

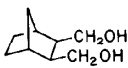

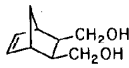

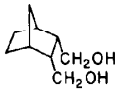

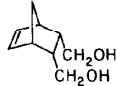

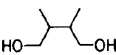

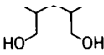

Chemical oxidations of diols to racemic lactones can be achieved by a broad spectrum of oxidizing agents.⁷ However, at the present time, only the enzymic route described can provide a versatile, one-step, access to such a wide range of highly enantiomerically enriched γ -lactones, useful as chiral building blocks for syntheses.

The lactones which have thus far been obtained by this route have been assembled in the Table. Each oxidation proceeds in high chemical yield (65-90%) to give products of > 97% enantiomeric excess.⁵

TABLE I

PREPARATION OF γ -LACTONES BY HLADH-CATALYZED OXIDATIONS
OF MESO-DIOLS (YIELD^{ref.}).

The optical purities and/or enantiomeric excesses were determined by ^1H NMR to be > 97%;⁵ **2** was obtained with 85% e.e.

	 1 (90% ¹⁶)		 2 (80% ⁴)
	 (72% ¹⁶)		 (81% ⁹)
	 (68% ¹⁶)		 3 (71% ¹⁶)
	 4 (87% ⁹)		 5 (64% ⁹)
	 (73% ⁹)		 (74% ⁹)
	 (86% ⁹)		 6 (64% ⁹)
	 (65% ¹⁶)		 7 (65% ¹⁶)

The maximum reaction time required for any one of the substrates shown in the Table is 7 days. In reaction mixtures which contain lactones 4 and 5, minor amounts of the hemiacetal intermediates are present; they are removed during the extraction at pH 13. After chromatographic separation from any unreacted diols, they can be readily converted to the corresponding lactones by chemical oxidation with silver carbonate on Celite.⁸

The lactones shown in the Table include several representatives of recognized or potential value as starting materials in natural product synthesis. Lactone 1 is a precursor of grandisol,^{9,10} lactone 3 of some pyrethroids,^{9,11} lactone 6 of some prostaglandins,^{9,12} and lactone 7 of multistriatin,¹³ methynolide¹⁴ and monensin.¹⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(+)-(1R, 6S)-8-Oxabicyclo[4.3.0]nonan-7-one: 1(3H)-Isobenzofuranone, hexahydro-, (3aS-cis)- (9); (65376-02-5)

cis-1,2-Bis(hydroxymethyl)cyclohexane: 1,2-Cyclohexanedimethanol, cis- (8,9); (15/53-50-1)

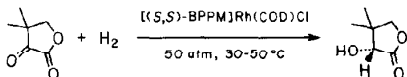
β -NAD; β -Nicotinamide adenine dinucleotide: Pyridinium, 3-carbamoyl-1- β -D-ribofuranosyl hydroxide, 5' \rightarrow 5' - ester with adenosine 5'-(trihydrogen pyrophosphate), inner salt (8); Adenosine 5'-(trihydrogen diphosphate), 5' \rightarrow 5' ester with 3-(aminocarbonyl)-1- β -D-ribofuranosylpyridinium hydroxide, inner salt (9); (53-84-9)

FMN; Flavin mononucleotide as sodium salt: Riboflavine 5'-(dihydrogen phosphate), monosodium salt (8,9); (130-40-5)

ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE:

D-(-)-PANTOYL LACTONE

(2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-)



Submitted by I. Ojima, T. Kogure, and Y. Yoda.¹

Checked by Larry K. Truesdale, Stanley D. Hutchings, and Gabriel Saucy.

1. Procedure

A. *Preparation of catalyst solution.* A 250-mL round-bottomed flask fitted with a septum and magnetic stirring bar is charged with 486.9-488.2 mg (Note 1) ($0.985\text{-}0.990 \times 10^{-3}$ mol) of chloro(1,5-cyclooctadiene)rhodium (I) dimer (Note 2) and, under argon (Note 3), with 1.20 g (2.15×10^{-3} ml) of (2S,4S)-N-tert-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM (Note 4). The sealed flask is charged by cannula, under argon, with 150 mL of degassed benzene (Note 5) and stirred under argon for 15 min at room temperature. The catalyst is transferred by cannula, under argon, into the autoclave (see below).

B. *Asymmetric hydrogenation*. A stainless steel stirred autoclave with a total volume of 500 mL is charged with 25.6 g (0.2 mol) of ketopantoyl lactone (Notes 6-9). The autoclave is flushed with argon and the catalyst solution (see above) is added by cannula, under argon. The autoclave is sealed and hydrogenation is carried out at 40°C, 150 psig hydrogen and 950-1050 rpm for 48 hr (Note 10). Care should be taken to flush all the lines before connecting to the autoclave. After the autoclave is cooled to room temperature, it is vented and opened. The reaction mixture is then transferred to a 500-mL, round-bottomed flask and most of the solvent is removed by rotary evaporator. Distillation (Note 11) of this reddish solid affords 24-25.6 g (92-98%) (Note 11) of D-(-)-pantoyl lactone: bp 90-110°C (4 mm); $[\alpha]_D^{25}$ -39.3° to -42.4° (c 2, H₂O) (Note 12) (78 to 84% ee) (Notes 1, 10).

The pantoyl lactone thus obtained (25.41 g), $[\alpha]_D^{25}$ -40.8° (80.5% ee) (Note 13) is refluxed with 75 mL benzene and 290 mL of H₂O-grade hexanes. The cloudy solution is stirred briskly overnight as solids form. Filtration of the solids and drying for 3 hr at 0.25 mm, 30°C in a vacuum oven affords 21.51 g of product: $[\alpha]_D^{25}$ -47.7° (94.27% ee). This material is again refluxed and crystallized (Note 14) from 30 mL of benzene and 116 mL of UV-grade hexanes to afford 19.97 g (77%) of product; $[\alpha]_D^{25}$ -49.87° (98.5% ee); Anal. Calcd for C₆H₁₀O₃: C, 55.37; H, 7.75. Found: C, 55.34; H, 7.57 (Note 15).

2. NOTES

1. The reaction was done four times at this scale. The range represents the high and low amounts of catalyst precursor used over the four reactions.

2. Chloro(1,5-cyclooctadiene)rhodium (I) dimer is commercially available from Strem Chemicals, Inc., Newburyport, MA.

3. The addition and measurement of (S,S)-BPPM is most conveniently done in a dry box or glove bag under argon. A Schlenk tube apparatus can be used if these are not available.

4. (2S,4S)-N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM,^{2,3} is commercially available from Chemical Dynamics Corp., South Plainfield, NJ.

5. The submitter claims that tetrahydrofuran can also be used giving D-(-)-pantoyl lactone with 83.3-84.8% ee. This was not checked.

6a. Ketopantoyl lactone is readily prepared by the oxidation of *d*,*L*-pantoyl lactone (Note 8) with bromine as follows.⁴ Into a 500-mL round-bottomed flask fitted with a mechanical stirrer, dropping funnel, condenser and thermometer is charged 13.0 g (0.1 mol) of *d*,*L*-pantoyl lactone (Note 7) and 150 mL of carbon tetrachloride. The mixture is stirred and heated to reflux. Bromine (16.5 g, 0.103 mol) in 100 mL of carbon tetrachloride is slowly added from the dropping funnel over 3 hr. After 8 hr, generation of hydrogen bromide subsides and the red color of bromine almost disappears, indicating completion of the reaction. Dry air is bubbled through the solution to remove the remaining hydrogen bromide and the small quantity of bromine. The solvent is removed with a rotary evaporator and further evacuated with a vacuum pump to afford 12.8 g (100%) (Note 9) of almost pure ketopantoyl lactone. One recrystallization from 150 mL of carbon tetrachloride (heat to reflux and then cool to -10°C) affords 11.6-12.2 g (90-95%) of pure ketopantoyl lactone, mp 66-67.5°C.

6b. An alternative procedure preferred by the checkers to prepare highly pure ketopantoyl lactone follows: A 5-L, round-bottomed flask equipped with a mechanical stirrer, condenser, thermometer, and dropping funnel is charged with 700 g of $\text{Ca}(\text{OCl})_2$ (analyzed as 20% active chlorine) and 1.5 L of acetonitrile dried overnight over 4Å sieves. *d,L*-Pantoyl lactone (165 g) (Note 7) is dissolved in 500 mL of dried acetonitrile. The $\text{Ca}(\text{OCl})_2$ slurry is stirred while ~ 1/7 of the pantoyl lactone solution is added. The temperature of the exothermic reaction is controlled with an ice bath to below 35°C. The remainder of the pantoyl lactone solution is added in ~ 75-mL aliquots over 25-30 min taking care to control the temperature. The ice bath is removed and stirring is continued. After 3.5 hr, GLC analysis indicates 94% product. The reaction mixture is filtered and the solids are rinsed with acetonitrile. The crude product is dried on a rotary evaporator and further evacuated overnight to yield 105.6 g. The material is dissolved in methylene chloride, dried over Na_2SO_4 , filtered through Celite and concentrated under reduced pressure. The crude product (94.1 g) is then purified by refluxing and stirring overnight with 500 mL of ethyl ether. The slurry is allowed to stand at 5°C. The solids are filtered, washed with cold ether, and dried in a vacuum oven at room temperature for 6 hr to afford 80.8 g (86% recovery) of pure ketopantoyl lactone.

Ketopantoyl lactone has also been reported to be easily prepared by the oxidation of *d,L*-pantoyl lactone with alkaline metal hypochlorite⁵ or by reaction of sodium dimethylpyruvate with formaldehyde in the presence of potassium carbonate.⁶

7. *d,L*-Pantoyl lactone is very hygroscopic. Care must be taken during this oxidation that dry starting material is used and that water does not contaminate the reaction; the yield will fall drastically probably because of hydrolysis.

8. *d,L*-Pantoyl lactone is commercially available from Sigma Chemical Company, St. Louis, MO 63178.
9. GLC analysis indicates 97-98% yield. A simple GLC system to determine the relative completion of the reaction is a 3 ft x 1/8 in column packed with 10% carbowax 20 M on Anakrom Q 90/100. With this column a program of 150° to 210°C at 8°/min and a 7-min hold, gives baseline separation of ketopantoyl lactone at 2.75-3.2 min and pantoyl lactone at 3.7-3.95 min. The flow rate of the carrier gas is 20 mL/min.
10. When ketopantoyl lactone prepared by method 6b was used, the reaction was complete in 2 hr.
11. A bulb-to-bulb distillation using a Kugelrohr apparatus is most convenient.
12. The reported maximum rotation, $[\alpha]_D^{25}_{\text{max}}$, for pure D-(-)-pantoyl lactone is -50.7° (c 2.05, H₂O).⁷
13. The enantiomeric excess and the speed of reduction are both greatly influenced by impurities that are not detectable by GLC. Digestion in ether seems to remove these impurities better than recrystallization from CCl₄.
14. This recrystallization is very temperature sensitive, e.g., this purification was done at ambient temperature (28-30°C). The first recrystallization removes 3.7 g of *d,L*-pantoyl lactone and 0.2 g of D-(-)-pantoyl lactone. When the recrystallization was done at 5°C, twice as much solvent served to remove only 4.2 g of *d,L*-pantoyl lactone and none of the D-isomer.
15. The procedure described is a scaled-up version (20 x) of the original submission worked out by the checkers.

3. Discussion

D-(-)-Pantoyl lactone is a key intermediate for the synthesis of pantothenic acid which is a member of the vitamin B-complex and is an important constituent of Coenzyme A. Although D-(-)-pantoyl lactone has been obtained by classical optical resolution using quinine, ephedrine, and other chiral amines, catalytic asymmetric synthesis appears to be more effective from a practical point of view.⁸ One problem of the present approach was the availability of ketopantoyl lactone, but the recent method developed by Hoffmann-La Roche⁶ comprising the condensation of sodium dimethylpyruvate with formaldehyde may open a commercial route to ketopantoyl lactone. Thus, asymmetric reduction of ketopantoyl lactone now becomes an important route to D-(-)-pantoyl lactone. Asymmetric reduction of ketopantoyl lactone can also be achieved with microorganisms. For example, microbial reduction of ketopantoyl lactone using baker's yeast was reported to give ca. 72% ee,⁹ and the specific strain of an ascomycete, *Byssoschlamys fulva*, was reported to give D-(-)-pantoyl lactone with 95-100% ee.⁹ However, the isolation procedure from aqueous media in these microbial reductions, i.e., extraction, recovery of raw materials, and purification, is very troublesome because of the high solubility of the product in water. Consequently, the present method has considerable advantages from a synthetic point of view, e.g., (i) the yield of the reaction is virtually 100%, and (ii) isolation of the product is simple and convenient since the reaction is carried out in small amounts of nonaqueous media.

The present method has been successfully applied¹⁰ to the asymmetric reduction of various α -keto carboxylates and α -keto lactones.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ketopantoyl lactone: 2,3-Furandione, dihydro-4,4-dimethyl (8,9); (13031-04-4)

D-(-)-Pantoyl lactone: 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-,

D- (8); 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl- (9); (599-04-2)

Chloro(1,5-cyclooctadiene)rhodium (I) dimer: Rhodium, di- μ -chlorobis(1,5-

cyclooctadiene) di- (8); Rhodium, di- μ -chlorobis[(1,2,5,6-)-1,5-

cyclooctadiene] di- (9); (12092-47-6)

(2S,4S)-N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-

methylpyrrolidine: 1-Pyrrolidinecarboxylic acid, 4-(diphenylphosphino)-2-

[(diphenylphosphino)methyl]-, 1,1-dimethylethyl ester, (2S-cis)- (9);

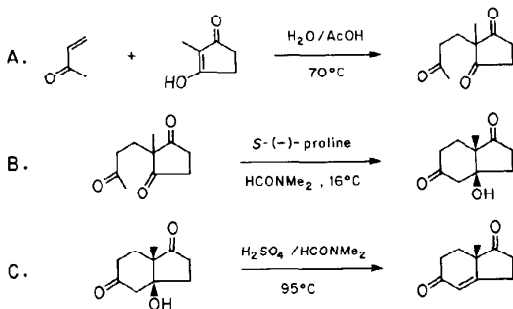
(61478-28-2)

d,*L*-Pantoyl lactone: 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-. (\pm)-

(8,9); (79-50-5)

(+)-(7aS)-2,3,7,7a-tetrahydro-7a-methyl-1H-indene-1,5-(6H)-dione

(1H-Indene-1,5(6H)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (S)-)



Submitted by Zoltan G. Hajos¹ and David R. Parrish.²

Checked by Stuart Remington, David Lust, and Gabriel Saucy.

1. Procedure

A. *2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione*. A 1.0-L, three-necked, round-bottomed flask equipped with a condenser, magnetic stirring bar and thermometer is charged with 112.1 g (1.0 mol) of 2-methyl-1,3-cyclopentanedione (Note 1), 230 mL of deionized water, 3.0 mL of glacial acetic acid, and 140 mL (120.96 g, 1.72 mol) of methyl vinyl ketone (Note 2). The system is shielded from light with aluminum foil and placed under a slight positive pressure of nitrogen. The flask is placed in an oil bath and

the temperature is raised to 70°C. The reaction is monitored by gas chromatography (GLC, Note 3) until complete (1-2 hr). The mixture is cooled, transferred to a separatory funnel and extracted with 500 mL and then two 100-ml portions of dichloromethane. The combined extracts are washed with 500 mL and 100 mL of saturated brine. The combined brine wash is extracted with a further two 100-mL portions of dichloromethane. The total dichloromethane extract is dried over sodium sulfate and filtered. The solvent is removed on a rotary evaporator at 45°C (70 mm). Drying on the rotary evaporator at 40-45°C (0.03 mm) for 16 hr gives 181.8 g (100%) of the desired triketone as an orange oil (Notes 4,5).

B. (+)-(3*a*S,7*a*S)-2,3,3*a*,4,7,7*a*-Hexahydro-3*a*-hydroxy-7*a*-methyl-1*H*-indene-1,5(6*H*)-dione. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet is charged with 188 mL of N,N-dimethylformamide (Note 6) and 863 mg (7.5 mmol) of 3-(-)-proline (Notes 7,8). The mixture is degassed four times by alternate evacuation and refilling with nitrogen. The system is shielded from light with aluminum foil and the contents of the flask are stirred in a 15-16°C bath (Note 9) for 1.0 hr. To the resultant suspension is added 45.5 g (0.25 mol) of the 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione prepared in step A. A total of 62.5 mL of N,N-dimethylformamide is used to insure complete transfer. The degassing procedure is repeated four times and stirring at 15-16°C (Note 10) is continued for 40-120 hr (Note 11) as the mixture becomes yellow and then brown. The reaction is monitored for completeness by thin layer chromatography (TLC, Note 12). The solution of the desired ketol (Note 13) is used directly in step C.

C. (+)-(7aS)-2,3,7,7a-Tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione. A

100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing dropping funnel and a nitrogen inlet is charged with 50 mL of N,N-dimethylformamide (Note 6). The contents of the flask are cooled to -20°C with a dry ice-acetone bath and 2.70 mL (4.97 g, 48.6 mmol) of concd sulfuric acid is added over 5-10 min at a rate to maintain a temperature of -15 to -20°C (Note 14).

The flask containing the solution of the (+)-(3aS,7aS)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione in N,N-dimethylformamide is placed in an oil bath and heated to 95°C. When the temperature reaches 70-75°C, an 18.8-mL aliquot of the concd sulfuric acid in N,N-dimethylformamide solution is added in one portion. The reaction mixture is heated to 95°C for 3.0 hr. After 1.0 hr, an additional 7.5-mL aliquot of the concd sulfuric acid in N,N-dimethylformamide solution is added in one portion. The reaction is monitored for completeness by GLC (Note 15) and cooled. The solvent is removed on a rotary evaporator at 45°C (0.3-0.5 mm) to give a brown oil. The material is taken up in 375 mL of dichloromethane. The solution is washed with two 190-mL portions of 2.0 N sulfuric acid solution which have been saturated with sodium chloride, two 190-mL portions of saturated sodium bicarbonate solution which have been saturated with sodium chloride and 190 mL of saturated brine. Each aqueous wash is extracted, in turn, with the same two 190-mL portions of dichloromethane. The combined dichloromethane solutions are dried over sodium sulfate, filtered, and the solvent is removed on a rotary evaporator at 40°C (70 mm) to give 38.8-39.6 g of oily, brown semisolid. This material is taken up in 78 mL of ethyl acetate and the solution is applied to a dry column of 78 g of silica gel (Note 16). The column is eluted with 600 mL of ethyl acetate and the total eluate is

stripped of solvent on a rotary evaporator at 40°C (70 mm) to give 37.2-38.8 g of tan crystalline solid. The solid is subjected to bulb-to-bulb distillation³ (Note 17) at 120-135°C (0.1 mm) to give 35.9-36.9 g of a slightly yellowish (cream white) solid, mp 56-61°, $[\alpha]_D^{25} +324-329^\circ$ (toluene, d 1.0) (Notes 18,19,20). This material is taken up in 74 mL of ether at reflux: The solution is brought at reflux to the point of turbidity with 19 mL of hexanes. The mixture is seeded, allowed to stand at ambient temperature for 2 hr and then chilled in a 17°C water bath for 30 min (Note 21). The solid is collected by filtration on medium porosity sintered glass, washed with two 12-mL portions of cold (3°C) 1:1 v/v ether:hexanes and dried at 20°C (70 mm) to give 28.7-31.3 g (70-76%) of white crystalline solid (Note 22), mp 64-66°C, $[\alpha]_D^{25} +347.5-349^\circ$ (toluene, d 1.0) (Note 23), purity by GLC 99.4-99.5% (Notes 24,25,26).

2. Notes

1. 2-Methyl-1,3-cyclopentanedione, 90%, purchased from the Aldrich Chemical Company, Inc., was used. Material prepared according to Hengartner, U.; Chu, V. *Org. Synth.* **1979**, *58*, 83-85 was determined by the checkers to be equally satisfactory.

2. Methyl vinyl ketone, technical grade, purchased from the Aldrich Chemical Company, Inc., was fractionally distilled into ca. 1% w/v hydroquinone shortly before use. The fraction boiling at 33-36°C (120 mm) was used.

3. Analyses were carried out on a Hewlett Packard HP 5840 A gas chromatograph operated isothermally at 150°C. A 25-m capillary column packed with crosslinked phenylmethylsilicone was employed. 2-Methyl-1,3-cyclopentanedione and 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione had retention times of ca. 7 min and 12.5 min, respectively.

4. If desired, pure triketone can be isolated by distillation of the crude triketone through a Vigreux column. The yield of light yellow oil, bp 115-120°C (0.2-0.3 mm), is 80-89%.

5. The triketone has the following spectral properties: IR (neat) cm^{-1} : 1770, 1725; ^1H NMR (CDCl_3) δ : 1.12 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3CO), 2.8 (m, 4 H), $\text{COCH}_2\text{CH}_2\text{CO}$).

6. N,N-Dimethylformamide, purchased from the Fisher Scientific Co., was mixed with 10% v/v toluene and distilled at atmospheric pressure. After all of the toluene had been distilled (head temperature to 148°C), vacuum was cautiously applied. The fraction of N,N-dimethylformamide which distilled at 78-82°C (56-64 mm) was collected and stored under nitrogen prior to use.

7. L-(-)-Proline [(S)-configuration], 99⁺%, purchased from the Aldrich Chemical Company, Inc., was employed. The material was finely ground in a mortar and pestle immediately before use.

8. The L-(-)-proline was established by the checkers to be of >99.8% (estimated level of detection) enantiomeric purity by conversion to N-pentafluoropropionyl-L-(-)-proline isopropyl ester and GLC analysis on a 50-m glass capillary column containing the chiral phase, Chirasil-Val (Quadrex Inc.). Analyses were performed on a Hewlett-Packard HP 5710 A instrument operated isothermally at 140°C. Racemic proline was used as a control.

9. The checkers used a flask with a built-in jacket. Water at 15-16°C was continuously circulated through the jacket.

10. Temperature control in this reaction is critical. At higher temperatures, the enantioselectivity of the reaction drops off significantly, while at lower temperatures, the reaction time becomes unacceptably long.

11. The reaction time varied substantially from run to run, but generally complete conversion was observed in 48-72 hr.

12. E. Merck silica gel F-254 plates were used, with 20:1 v/v dichloromethane : methanol as eluent. The plates were developed by drying, spraying with 9:1 v/v deionized water:concentrated sulfuric acid, light drying with a hot air gun, spraying with 3% w/v vanillin solution in ethanol and strong heating with the hot air gun. The approximate R_f values observed were 0.67 (starting triketone) and 0.37 (product ketol). In addition, a minor spot at R_f 0.59 (enone arising from dehydration of the ketol) was seen.

13. If desired, the ketol can be isolated as follows. The reaction mixture from 18.0 g of distilled 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione is evaporated on a rotary evaporator at 45°C (0.3 mm) to give 22.0 g of brown oil. A solution of this material in 200 mL of ethyl acetate is filtered through 80 g of J. T. Baker silica gel. Elution with ca. 1.3 L of ethyl acetate in 200-mL fraction is monitored by TLC (Note 12). The fractions containing the desired product are combined and stripped of solvent on a rotary evaporator at 45°C (70 mm). Final drying on the rotary evaporator at 45°C (0.3 mm) gives 18.0 g (100%) of crude ketol as a slightly oily, brown solid having the following spectral properties: IR (CHCl_3) cm^{-1} : 3600, 3500-3300, 1742, 1722; ^1H NMR (CDCl_3) δ : 1.26 (s, 3 H, CH_3), 2.63 (s, 2 H, COCH_2COH). Further purification of the compound by crystallization from ether (ca. 50% recovery) gives material of mp 118-119°C, $[\alpha]_D^{25} +59.8^\circ$ (lit⁴ mp 119-119.5°C, $[\alpha]_D^{25} +60.4^\circ$).

14. The solution is prepared immediately before use and kept at -20°C.

15. The GLC system described in Note 3 was employed. The intermediate ketol and product enone had retention times of ca. 23 min and 16.5 min, respectively. A trace of ketol (<1%) is observed at the end of the reaction.

16. E. Merck silica gel 60 (70-230 mesh) was used. The column dimensions were 3.2 x 60 cm.

17. A Kugelrohr apparatus, purchased from the Aldrich Chemical Company, Inc., was used. The receiving bulb was cooled with an ice-water bath. The temperature indicated is that of the oven air bath.

18. The ratio of rotations obtained in toluene and benzene has been determined to be 1.00:1.03. The rotation of enantiomerically pure material in toluene, based on the accepted⁴ value of +362° in benzene, is 351°. The enantiomeric purity at this stage is thus 92-94% (Note 19).

19. Attempts by both the submitters and checkers to find a method other than optical rotation to determine the enantiomeric purity have been unsuccessful.

20. Material of this purity is satisfactory for many synthetic purposes, cf. reference 3.

21. Further cooling results in a higher recovery of material. However, the melting point and rotation of the samples thus obtained are lower.

22. The compound is somewhat unstable. It is best stored in an amber bottle under nitrogen at 3°C.

23. The enantiomeric purity of the purified material is thus 99.0-99.4% (cf. Note 18).

24. GLC analysis was carried out on a Hewlett Packard HP 5710 A gas chromatograph operated isothermally at 155°C. A 50-m capillary column of OV-17 on fused silica was employed. The enone had a retention time of ca. 14.5 min.

25. The material has the following spectral properties: UV (CH_3OH) λ 235 nm ($\epsilon = 11,200$); IR (CHCl_3) cm^{-1} : 1746, 1665; ^1NMR (CDCl_3) δ : 1.31 (s, 3 H), 7a- CH_3), 5.97 (broad, s, 1 H, vinylic-H).

26. Steps B and C have been scaled up to the 2.0-mol level with no loss in yield or enantiomeric purity.

3. Discussion

The (S)-(-)-proline catalyzed asymmetric aldol cyclization of the triketone to the optically active bicyclic aldol product, followed by dehydration to the optically active enedione, (+)-(7aS)-2,3,7,7a-tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione, has been described, and two alternative reaction mechanisms have been suggested by the submitters.⁵ The exact mechanism of the extremely high asymmetric induction in the crucial conversion of the prochiral triketone to the optically active ketol still needs to be clarified.^{6a,b,c}

The synthesis of the triketone has been included (Part A of the Procedure), since identification of the crystalline compound originally claimed⁷ to be the triketone has been shown to be in error.⁸ After completion of our work, the triketone was correctly characterized by another research group.⁹

Asymmetric aldol cyclization of the triketone with (S)-(-)-proline can also be effected in solvents other than N,N-dimethylformamide; acetonitrile is outstanding.⁵

Of the asymmetric amino acid reagents investigated, (S)-(-)-proline gave the highest optical yield (93.4%); (-)-trans-4-hydroxyproline gave 73.1%, and (S)-(-)-azetidinecarboxylic acid gave 63.9% optical yields in the asymmetric synthesis of the optically active bicyclic ketol.

The use of (R)-(+)-proline in acetonitrile induced the asymmetric aldol cyclization of the triketone to the enantiomeric ketol, (-)-(3aR,7aR)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione.¹⁰

The ethyl homolog of the triketone, 2-ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione, has been converted with (S)-(-)-proline in N,N-dimethylformamide to (+)-(3aS,7aS)-7a-ethyl-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-1H-indene-1,5(6H)-dione in good yield.⁵ This in turn could be dehydrated to the homologous bicyclic enedione, (+)-(7aS)-7a-ethyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione.⁵

Circular dichroism studies of the 7a-methyl bicyclic ketol suggested, and a single-crystal X-ray diffraction study of the racemic compound confirmed, the cis conformation with an axial 7a-methyl and an equatorial 3a-hydroxy group in the six-membered ring of the bicyclic system. On the other hand, similar measurements of the 7a-ethyl bicyclic keto established the alternate possible cis conformation to avoid the 1,3-diaxial interactions between the angular ethyl group and the C-4 and C-6 axial hydrogens.

Dehydration of the optically active bicyclic ketols in refluxing benzene with a little p-toluenesulfonic acid could readily be effected without loss of optical purity.⁵ It has been shown by a research group at Schering A. G., Berlin, Germany that the triketone can be converted directly to the optically active enedione with 0.5 eq. of (S)-(-)-proline and 0.25 eq. of 1 N aqueous HClO₄ in refluxing acetonitrile.¹¹

The optically active bicyclic enedione, (+)-(7aS)-2,3,7,7a-tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione, was prepared first by microbiological means,⁴ and its absolute stereochemistry has been established.¹² The compound was later prepared by optical resolution.¹³

The products of this highly efficient asymmetric synthesis are important intermediates in natural product chemistry, e.g., the total synthesis of steroids and prostaglandins.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-(7a*S*)-2,3,7,7a-Tetrahydro-7a-methyl-1*H*-indene-1,5(6*H*)-dione: 1,5(6*H*)-Indanedione, 7,7a-dihydro-7a*β*-methyl-, (+)-(8); 1*H*-Indene-1,5(6*H*)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (*S*)-(9); (17553-86-5)

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione: 1,3-Cyclopentanedione, 2-methyl-2-(3-oxobutyl)- (8,9); (25112-78-1)

2-Methyl-1,3-cyclopentanedione: 1,3-Cyclopentanedione, 2-methyl- (8,9); (765-69-5)

Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

(+)-(3a*S*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1*H*-indene-1,5(6*H*)-dione: 1*H*-Indene-1,5(4*H*)-dione, hexahydro-3a-hydroxy-7a-methyl-, (3a*S*-cis)-(9); (33879-04-8)

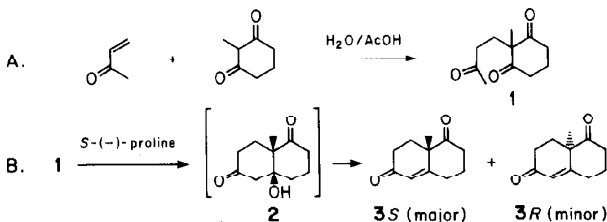
N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)

S-(-)-Proline: Proline, L- (8); L-Proline (9); (147-85-3)

ASYMMETRIC SYNTHESIS OF (S)-8a-METHYL-3,4,8,8a-

TETRAHYDRO-1,6(2H,7H)-NAPHTHALENEDIONE

(1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (S)-)



Submitted by Paul Buchschacher[†] and A. Fürst.¹

Checked by P. S. Belica, P. S. Manchand, and Gabriel Saucy.

1. Procedure

Caution! Part A should be performed in a well-ventilated hood because methyl vinyl ketone is a lachrymator.

A. 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione. A 1-L, round-bottomed flask equipped with a thermometer, and a reflux condenser capped with an argon-inlet tube, is charged with 126.1 g (1 mol) of 2-methyl-1,3-cyclohexanedione (Note 1) and 300 mL of distilled water. To the well-stirred suspension are added 3 mL of acetic acid, 1.1 g of hydroquinone, and 142 g (167 mL, 2 mol) of freshly distilled methyl vinyl ketone (Note 2). The reaction mixture is stirred under argon at 72-75°C for 1 hr, treated with

sodium chloride (103 g), and poured into a separatory funnel containing ethyl acetate (400 mL). The organic phase is collected and the aqueous phase is re-extracted twice with ethyl acetate (150 mL each time). The combined extracts are washed with two 200-mL portions of saturated brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate is evaporated at 40°C under reduced pressure (water aspirator) on a rotary evaporator. The residue is kept under high vacuum (1.0 mm) at 40°C for 30 min to give 210.8 g of crude 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (1, "trione") as a pale yellow oil, homogeneous by thin layer chromatography (Note 3). This crude material is used in Part B.

B. *(S)*-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione (3-S). A 3-L. one-necked, round-bottomed flask, equipped with an argon-inlet tube and containing a magnetic stirrer, is charged with 5.75 g (0.05 mol) of finely ground L-proline (Note 4), and a solution of 210.8 g of crude trione 1 (from Part A) in anhydrous dimethyl sulfoxide (Note 5). The mixture is stirred at room temperature (ca. 25°C) under argon for 120 hr, the magnetic bar is removed, and the solvent is removed under high vacuum (1.0 mm) at 65°C (Note 6) on a rotary evaporator to give 206.9 g of a dark reddish-violet oil. The oil is dissolved in toluene (100 mL) and is adsorbed on a column (9 cm x 60 cm) of silica gel (1.5 kg, 70-230 mesh) (Note 7), which was previously packed in hexane. Elution is carried out under a slight positive pressure of argon (ca. 1 atm) (Note 8) initially with 1 L of hexane:ethyl acetate (5:1) and then with a 3:2 mixture of hexane:ethyl acetate taking 300-mL fractions. The progress of the purification is monitored by thin layer chromatography (Note 9): no product is observed until ca. 5 L of eluant is collected. Fractions containing the product are combined, and the solvents are removed under reduced pressure (water aspirator) at 45-50°C. The residue is then kept

under high vacuum (0.1 mm) at 40°C for 30 min to give 154.2 g of an orange-colored oil, $[\alpha]_D^{25} +68^\circ$ (toluene, c 1.463). This material is dissolved in 535 mL of ether and is filtered through a fluted filter paper to remove small particles. The flask is rinsed with 500 mL of ether and this is passed through the filter paper. The combined filtrates are seeded with a few crystals of pure 3-S (Note 10), and the mixture is left at -20°C for 18 hr. Most of the supernatant liquid is carefully decanted without agitation, and the crystals are collected by filtration. The flask is rinsed with cold (0°C) 50% ether in hexane and the rinse is used to wash the crystals. The crystals are melted at 55°C under reduced pressure (12 mm) on a rotary evaporator and allowed to crystallize at 25°C to yield 85.9 g of (S)-enedione (first crop), mp 49-50°C, $[\alpha]_D^{25} +96.91^\circ$ (toluene, c 1.1743) (Note 11). The combined filtrate and washings are evaporated to give 67.1 g of an orange-colored oil, which is dissolved in 604 mL of ether, cooled to 3°C, and seeded with (R,S)-enedione (Note 12). The mixture is left at -20°C for 18 hr, and the supernatant liquid is carefully decanted (no agitation). The wet crystals are then collected by filtration, washed with cold (0°C) 50% ether in hexane, and dried under reduced pressure at room temperature to give 36.3 g of racemic material (3R + 3S). The filtrate and washing are evaporated to give 30.6 g of an oil, which is dissolved in 100 mL of ether and filtered through a fluted filter paper. The flask is rinsed with 114 mL of ether, filtered through the fluted filter paper, and the combined filtrates are cooled to 3°C and seeded with crystals of the pure 3-S. The mixture is left at -20°C overnight, the supernatant liquid is carefully decanted without much agitation and the wet crystals are collected by filtration and washed with cold (0°C) 50% hexane in ether. The product is melted under reduced pressure (12.0 mm) at 55°C and allowed to crystallize at room temperature to give 15.3 g of light amber-

colored crystals (second crop), mp 49-50°C, $[\alpha]_D^{25} +97.3^\circ$ (toluene, d 1.05). The total yield of (S)-enedione is 101.2 g (56.8%) (Note 13).

2. Notes

1. 2-Methyl-1,3-cyclohexanedione² was obtained from Aldrich Chemical Company, Inc. and had mp 208-210°C.
2. Methyl vinyl ketone, bp 34°C/120 mm, was obtained from Aldrich Chemical Company, Inc.
3. Thin layer chromatography was performed on silica gel with ethyl acetate:hexane (3:2). Visualization of the spots was achieved by spraying the plates with 10% ceric sulfate in 10% sulfuric acid, heating the plates to ca. 120°C, and spraying again with 10% phosphomolybdic acid in isopropyl alcohol. The product has R_f 0.50; 2-methyl-1,3-cyclohexanedione has R_f 0.30.
4. S-(-) Proline was obtained from Aldrich Chemical Company, Inc.
5. Dimethyl sulfoxide was dried over molecular sieves type 4 Å. Anhydrous N,N-dimethylformamide was used by the submitter; cf. ref. 3.
6. The temperature should be kept below 70°C.
7. Silica gel was purchased from EM Reagents, E. Merck, Darmstadt, Germany.
8. The procedure of W. C. Still⁴ is used.
9. Silica gel and 60% ethyl acetate in hexane were used. The product, R_f 0.40, is visible under short wavelength ultraviolet light whereas the starting trione, also R_f 0.40, is not. Visualization is achieved as described in Note 3.
10. Compound 3-S was obtained from material having $[\alpha]_D^{25} +68^\circ$ (toluene, d 1.60) that was prepared in another experiment. Thus, 28.2 g of this (S)-

enedione is dissolved in 90 mL of ether and the solution is left at -20°C for 18 hr. The crystals are collected by filtration without much agitation, washed with 30 mL of cold (0°C) 50% ether in hexane, and redissolved in 117 mL of ether. The solution is left at -20°C for 18 hr, and the crystals are collected by filtration, washed with 30 mL of cold (0°C) 50% ether in hexane, and dried under reduced pressure (1.0 mm) at room temperature to give 12.0 g of (S)-enedione, mp 50°C , $[\alpha]_{\text{D}}^{25} +100^{\circ}$ (benzene, c 1.461). It should be possible to prepare seed crystals from a small aliquot, but this was not attempted by the checkers.

11. This assures consistency of material.

12. Racemic Wieland-Miescher ketone was obtained from Aldrich Chemical Company, Inc. or prepared according to the procedure of Ramachandran and Newman.⁵

13. ^1H NMR studies (100 MHz, CDCl_3) using the shift reagent tris[3-(heptafluoropropyl)hydroxymethylene]-d-camphorato]europium(III) (purchased from Aldrich Chemical Company, Inc.) indicated that the two crops were enantiomerically pure. Under identical conditions (10 mg of reagent per 9.6 mg of substrate), absorption due to the vinyl proton at δ 5.86 in the racemate appeared as two peaks (1 Hz separation) of equal intensity.

3. Discussion

Racemic 8a-methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione (the Wieland-Miescher ketone)^{5,6} is a versatile building block for the synthesis of steroids⁷ and terpenoids.⁸ The (S) enantiomer, 3-S, was first obtained by microbiological means⁹ and by classical resolution via a derived hemiphthalate.¹⁰ The present synthesis³ of 3-S is based¹¹ on the asymmetric

intramolecular aldolization of the prochiral triketone 1 using S-(-)-proline catalytically. The product is obtained in 56% yield (from 2) and is enantiomerically pure based on optical rotation and on NMR spectroscopy determined in the presence of a chiral shift reagent. Despite numerous synthetic investigations and modifications of this asymmetric Robinson annulation,¹² the mechanism of enantiodifferentiation is still not fully understood;¹³ cf. discussion in the preceding procedure relating to the asymmetric synthesis of the corresponding S-(+)-tetrahydro-1-methylindenedione.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-(S)-(+) - (8); 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (S)- (9); (33878-99-8)

2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione: 1,3-Cyclohexanedione, 2-methyl-2-(3-oxobutyl)- (9); (5073-65-4)

2-Methyl-1,3-cyclohexanedione: 1,3-Cyclohexanedione, 2-methyl- (8,9); (1193-55-1)

L-Proline: Proline, L- (8); L-Proline (9); (147-85-3)

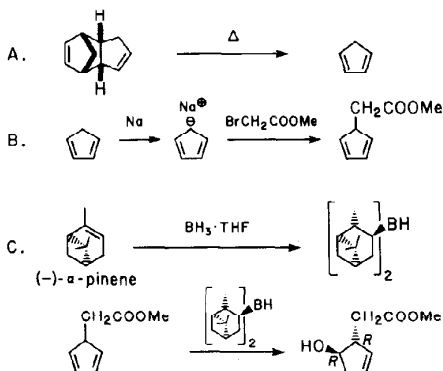
Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl- (8,9); (20007-72-1)

ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES:

SYNTHESIS OF METHYL (1R,5R)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE

(2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)-)



Submitted by John J. Partridge, Naresh K. Chadha, and Milan R. Uskoković.¹

Checked by Bai Dong-lu and Clayton H. Heathcock.

1. Procedure

A. *Pyrolysis of dicyclopentadiene to form cyclopentadiene.* Cyclopentadiene is prepared from its dimeric form by distillation according to the method of Moffett.² The apparatus for the distillation is assembled as shown in Diagram 1. The equipment consists of a 250-mL flask, a Friedrichs condenser fitted with a Haake Model FE hot water circulator, a Claisen head, a thermometer, a gas inlet tube, and a collection receiver which is cooled to -78°C in a dry ice-acetone bath.

In the 250-mL flask is placed 100 ml of dicyclopentadiene (Note 1). The material is heated at reflux (bath temperature 200-210°C) under a nitrogen atmosphere (Note 2). After a 5-mL forerun is collected and discarded, the collection receiver is cooled to -78°C and 25 mL (0.30 mol) of cyclopentadiene is rapidly distilled at bp 36-42°C. A slight positive pressure of nitrogen is maintained throughout the distillation to prevent moisture from entering the system.

The distilled cyclopentadiene is stored at -78°C until it is used (Note 3). Residual dicyclopentadiene can be reused until it solidifies on cooling.

B. *Preparation in situ of methyl 2,4-cyclopentadiene-1-acetate* (Note 4). Cyclopentadienylsodium is prepared by modification of the methods of King³ and Hafner⁴ (Note 5).

In a 500-mL, three-necked Morton flask fitted with a condenser, mechanical stirrer, and gas inlet tube is placed 8.6 g (0.375 g atom) of sodium and 75 ml of dry xylene (Note 6); the unstirred mixture is heated at reflux under a nitrogen atmosphere. After the xylene has reached its boiling point and the sodium has melted, the solution is rapidly stirred to produce a very fine-grained sodium sand. Quickly the heating mantle is removed and stirring stopped (Note 7). After cooling, the xylene is pipetted or siphoned away from the sodium sand and stored for future use.

The sand is washed with 3 x 25 mL of dry tetrahydrofuran (Note 8), then is layered with 100 mL of dry tetrahydrofuran, and the mixture is cooled to -10°C (Note 9) under a nitrogen atmosphere. A solution of 25 mL (0.30 mol) of cyclopentadiene in 25 mL of tetrahydrofuran is added dropwise using a dropping funnel. After the addition is complete, the mixture is stirred overnight at room temperature, by which time hydrogen evolution has ceased. In the absence of air, the solution ranges from near colorless to bright pink (Note 10).

In a 1-L, three-necked flask fitted with a 200-mL pressure-equalizing dropping funnel, mechanical stirrer, and a gas inlet tube, is placed 45.9 g (0.30 mol) of methyl bromoacetate (Note 11) and 15 mL of tetrahydrofuran and the mixture is cooled to -78°C in an inert atmosphere.

The solution of ca. 0.30 mol of cyclopentadienylsodium is decanted from residual sodium sand with a U-tube into the dropping funnel (Note 12) and is added dropwise over a 2-hr period (Note 13). A white precipitate of sodium bromide forms during the addition. The heterogeneous solution is stirred overnight at -70°C to insure complete formation of methyl 2,4-cyclopentadiene-1-acetate.

C. *Asymmetric hydroboration with (+)-di-3-pinanylboration to form methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate* (Note 4). The (+)-di-3-pinanylboration is prepared from (-)- α -pinene by a modification^{5,6} of the method of Brown⁷ (Note 14).

In a 2-L, three-necked flask fitted with a condenser, mechanical stirrer, and a gas inlet tube is placed 90.0 g (0.66 mol) of (-)- α -pinene (Note 15). The flask is cooled to 0°C and under an inert atmosphere a total of 300 mL (0.30 mol) of 1 M borane in tetrahydrofuran (Note 16) is added dropwise over a 1-hr period. The solution is stirred for 18 hr at 0°C during which time a white precipitate of (+)-di-3-pinanylboration forms. This solution is then cooled to -78°C . The ca. 0.30 mol solution of methyl 2,4-cyclopentadiene-1-acetate (Part B) is transferred at -78°C to a 500-mL pressure-equalizing dropping funnel through a U-tube in an inert atmosphere, and is added rapidly, in one portion, to the stirring solution of di-3-pinanylboration at -78°C . After this mixture is stirred for 6 hr at -78°C , the bath temperature is allowed to rise to 0°C and the mixture is stirred for 10 hr at 0°C to complete the hydroboration reaction.

To the reaction mixture is added dropwise 90 mL of 3 N aqueous sodium hydroxide, followed by 90 mL of 30% hydrogen peroxide (Note 17). The mixture is stirred for 30 min to complete the oxidation process. A total of 3 g of sodium bisulfite, 5 g of sodium chloride, and 125 mL of ether are added and the mixture is stirred for 10 min (Note 18). On standing, the reaction mixture separates into two layers, which are separated with a 1-L separatory funnel. The organic layer is washed with brine (2 x 50 mL). The water layer and the brine washes are combined and extracted with ether (3 x 125 mL). All the organic layers are then combined and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 110 g of a pale yellow oil containing the desired product as well as (+)-isopinocampheol and (-)- α -pinene (Note 19). The product mixture is dissolved in 250 mL of ether and is extracted with 1 M aqueous silver nitrate solution (3 x 100 mL). The aqueous layers are combined and back-extracted once with 50 mL of ether. The ether layers containing (+)-isopinocampheol are discarded.

The aqueous layers containing the silver(I) complex of methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate are then treated with an excess of saturated brine to precipitate silver chloride and free the desired product. After precipitation is complete, the water layer is decanted from the solid silver chloride. The solids are washed with ether (4 x 100 mL) and each ether layer is used to extract the water layer (Note 20). The combined ether layers are washed with 50 mL of brine and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 16-19 g of crude product. The product is distilled through a 4"-Vigreux column at 0.1 mm pressure to yield 12.8-14.7 g (27-31%) of methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate. bp 74-78°C at 0.1 mm. $[\alpha]_D^{25} -132^\circ$ (CH₃OH, c 1.06) (Notes 21, 22).

2. Notes

1. Dicyclopentadiene was obtained from Ace Scientific, (TX 315) practical grade, 95%.
2. The Haake water circulator was employed with the circulating water temperature at 50°C. This allows only cyclopentadiene to distill.
3. Cyclopentadiene is stable at -78°C but dimerizes readily at room temperature.
4. Steps B and C must be run concurrently.
5. The efficient formation of cyclopentadienylsodium is of paramount importance for the entire reaction sequence. Variations in the yield of methyl 2,4-cyclopentadiene-1-acetate have been traced to the degree of efficiency in producing a fine sodium sand which is used to produce cyclopentadienylsodium. In the alkylation reaction of cyclopentadienylsodium with methyl bromoacetate, the entire process must be carried out in an inert dry atmosphere at -78°C. At higher temperatures, the desired product can undergo undesired dimerization and double bond migration side reactions. Methyl 2,4-cyclopentadiene-1-acetate, once formed, is used immediately.
6. Xylene was obtained from Fisher Scientific Company. The xylene is initially dried over sodium and is saved and reused in making additional batches of sodium sand.
7. If stirring continues while the xylene cools, the sodium sand coagulates into a large lump.
8. Tetrahydrofuran was obtained from Fisher Scientific Company. The tetrahydrofuran employed was freshly distilled from lithium aluminum hydride. Care should be exercised in drying tetrahydrofuran; cf. *Org. Synth., Collect. Vol. V* 1973, 976. The checkers also examined the use of

tetrahydrofuran that had been dried by distillation from sodium/benzophenone ketyl. When material that has been purified in this manner is used, the fine sodium sand coagulates, giving small porous lumps. No such coagulation occurs when tetrahydrofuran that has been dried by distillation from lithium aluminum hydride is used. However, the method of drying had no effect on overall yield of final product.

9. A bath of carbon tetrachloride containing a little dry ice is used for cooling.

10. The efficient formation of cyclopentadienylsodium was found to be the product-limiting step for the reaction sequence. *If air is present or if the sodium sand is not fine-grained, quantitative formation of cyclopentadienylsodium cannot be assumed.* Residual sodium sand may be washed with tetrahydrofuran, dried in a nitrogen atmosphere and weighed to determine approximately the extent of cyclopentadienylsodium formation.

11. Methyl bromoacetate was obtained from Ace Scientific (MX 755).

12. Care must be taken during this transfer to minimize exposure of the cyclopentadienylsodium to air. Trace amounts of oxygen cause the formation of a dark brown color and brown solid in the solution.

13. The drip rate should be adjusted so that the dropping funnel is not plugged by crystalline cyclopentadienylsodium.

14. After the asymmetric hydroboration-oxidation sequence is completed, the desired product is separated via its silver(I) complex from (+)-isopinocampheol. The desired product can also be isolated by column chromatography.

15. (-)- α -Pinene was obtained from Chemical Samples Company. The (-)- α -pinene was distilled from sodium metal: bp 155-156°C; $[\alpha]_D^{25}$ -47° (neat).

16. Borane-tetrahydrofuran was obtained from Alfa Products, Morton/Thiokol Inc.

17. The hydrogen peroxide oxidation is a very exothermic process and efficient cooling and stirring are necessary.

18. After the addition of ether, some inorganic salts precipitate. The checkers found it advantageous to remove this solid by suction filtration. The solid was washed with ether, which was combined with the organic solution.

19. Vacuum distillation does not effectively purify the desired product from the other impurities.

20. Methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate is found in both the aqueous layer and occluded with the solid silver chloride.

21. In like manner and employing (+)- α -pinene [bp 155-156°C; $[\alpha]_D^{25} +47^\circ$ (neat)], the sequence affords the methyl (1S,5S)-5-hydroxy-2-cyclopentene-1-acetate, bp 74-77°C (0.1 mm); $[\alpha]_D^{25} +131^\circ$ (CH₃OH, c 1.03).

22. The checkers used (-)- α -pinene (bp 155°C, $[\alpha]_D^{22} -42^\circ$ (neat)) from Aldrich Chemical Company, Inc., and obtained a product having bp 75-80°C (0.15 mm) and $[\alpha]_D^{21} -126^\circ$ (CH₃OH, c 0.039).

3. Discussion

Several highly enantioselective asymmetric hydroboration reactions with prochiral olefins have been reported⁸ with the di-3-pinanylborane reagents (diisopinocampheylboranes) discovered by Brown and Zweifel.⁹ Recently, alternative reagents such as the mono-3-pinanylboranes (monoisopinocampheylboranes),^{10,11} and (+)-dilogifolylborane¹² have been used in effecting asymmetric hydroborations on prochiral olefins. With the di-3-pinanylborane reagents, cis-disubstituted olefins^{8,9} and 5-substituted cyclopentadienes^{5,6}

yield alcohols of high optical purity (80-95% ee). Lower asymmetric inductions (20-40% ee) occur when 1,1-disubstituted, trans-disubstituted, or trisubstituted olefins are employed as substrates. However, significantly higher enantioselective hydroborations occur when these olefins are treated with the mono-3-pinanylboranes^{10,11} and (+)-longifolylborane.¹² Tetrasubstituted olefins have not successfully been asymmetrically hydroborated with any of these reagents.

Several racemic cis- or trans-2-alkyl-3-cyclopenten-1-ols have been prepared by multistep sequences from cyclopentadiene¹³⁻¹⁶ or from substituted 1,3-dienes.¹⁷ However, optically active cis- and trans-2-alkyl-3-cyclopenten-1-ols have been prepared directly by asymmetric hydroboration reactions using prochiral 5-substituted cyclopentadienes as substrates.^{5,6} This asymmetric hydroboration method, described above, gives moderate yields of highly optically active trans-2-alkyl-3-cyclopenten-1-ols (94-96% ee) which are readily converted into the corresponding cis isomers.^{5,6} Several of these substances are intermediates in the synthesis of such natural products as the monoterpene glycoside loganin,⁵ the carbohydrate daunosamine,¹⁸ and the prostaglandins such as PGF_{2α}.⁶

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Diagram 1. Apparatus for Producing Cyclopentadiene

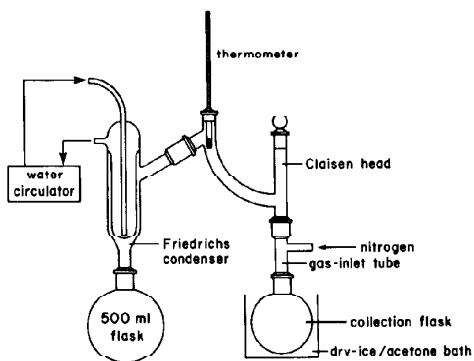
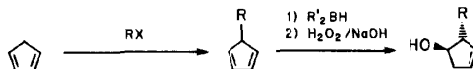


TABLE I

ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES



Substituent	Alkylating	Hydroborating	Yield	Absolute	%* Enantio- meric Excess	Reference
	Agent	Agent		Stereochemistry		
R = CH ₃	CH ₃ I	(+)-di-3-pinarylborane	40-50%	R,R	94-96%	(5), (19)
	CH ₃ I	(-)-di-3-pinarylborane	40-50%	S,S	94-96% ee	(5), (19)
	(CH ₃) ₂ SO ₄	(+)-di-3-pinarylborane	2%	R,R	----	(19)
R = CH ₂ CO ₂ CH ₃	BrCH ₂ CO ₂ CH ₃	(+)-di-3-pinarylborane	40-50%	R,R	94-96% ee	(6), (19)
	BrCH ₂ CO ₂ CH ₃	(-)-di-3-pinarylborane	40-50%	S,S	94-96% ee	(6), (19)
	ClCH ₂ CO ₂ CH ₃	(+)-di-3-pinarylborane	trace	R,R	----	(19)
R = CH ₂ CO ₂ -t-Bu	BrCH ₂ CO ₂ -t-Bu	(+)-di-3-pinarylborane	trace	R,R	----	(19)

*The percent enantiomeric excess was determined by HPLC analysis of products esterified with pure (S)- α -methoxy- α -trifluoromethylphenylacetyl chloride (Mosher Reagent),^{20,21}

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate: 2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)- (9); (49825-99-2)

Dicyclopentadiene: 4,7-Methanoindene, 3a,4,7,7a-tetrahydro- (8); 4,7-Methano-1H-indene, 3a,4,7,7a-tetrahydro- (9); (77-73-6)

Methyl 2,4-cyclopentadiene-1-acetate: 2,4-Cyclopentadiene-1-acetic acid, methyl ester (9); (37455-98-4)

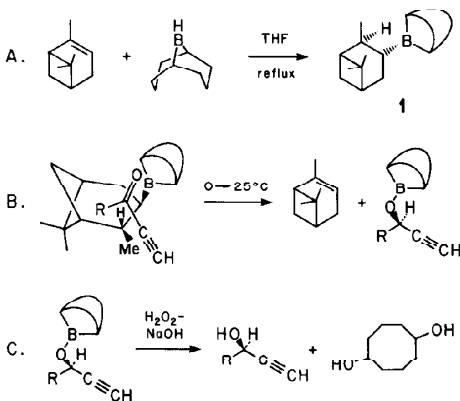
Methyl bromoacetate: Acetic acid, bromo-, methyl ester (8,9); (96-32-2)

(+)-Di-3-pinanylborane: Borane, di-3-pinanyl-, (+)- (8); Borane, bis (2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)-, [1 α ,2 α ,3 β (1R*,2R*,3S*,5S*), 5 α]-(+)- (9); (21947-87-5)

(-)- α -Pinene: 2-Pinene, (1S,5S)-(-)- (8); Bicyclo[3.1.1.]hept-2-ene, 2,6,6-trimethyl-, (1S)- (9); (7785-26-4)

Borane-tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1:1) (8,9); (14044-65-6)

**ASYMMETRIC REDUCTION OF α,β -ACETYLENIC KETONES WITH
B-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE: (R)-(+)-1-OCTYN-3-OL
(1-Octyn-3-ol, (R)-)**



Submitted by M. Mark Midland and Richard S. Graham.¹

Checked by Joel M. Hawkins and K. Barry Sharpless.

1. Procedure

A. A 2-L, round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser and stopcock adaptor connected to a mercury bubbler, is flame dried while being flushed with nitrogen. A nitrogen atmosphere is maintained during the procedure through the oxidation step. After the apparatus is cooled, it is charged, via a double-ended needle,² with

800 mL of a 0.5 M tetrahydrofuran (THF) solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 0.4 mol, Note 1). Then 61.3 g (71.5 mL, 0.45 mol) of (+)- α -pinene (Note 2) is added. After the solution is refluxed for 4 hr, the excess α -pinene and THF are removed by vacuum (Note 3) to provide a thick clear oil of neat 8-3-pinanyl-9-borabicyclo[3.3.1]nonane, **1** (Note 4).

B. The flask is cooled to 0°C (ice bath) and 35.3 g (0.285 mol) of 1-octyn-3-one (Note 5) is added. After an initially exothermic reaction, the reaction is allowed to warm to room temperature. The reduction can be monitored by gas chromatography (Note 6), but generally 8 hr is required for completion. The color of the reaction mixture is initially light yellow and darkens to red at the end of the reduction.

C. Excess **1** is destroyed by adding 22 mL (0.3 mol) of freshly distilled propionaldehyde and stirring for 1 hr at room temperature. Liberated α -pinene is then removed by vacuum (Note 7). Tetrahydrofuran, 200 mL, is added, followed by 150 mL of 3 M aqueous NaOH. Hydrogen peroxide (150 mL, 30%) is added dropwise (*CAUTION!* Note 8). Oxidation is complete in 3 hr at 40°C. The reaction mixture is transferred to a separatory funnel and extracted with three 50-mL portions of ethyl ether. The ether layers are combined and dried with copious amounts of anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give an oil. Distillation at 50–65°C (3.0 mm) yields 31 g (0.245 mol) of 1-octyn-3-ol, 86% yield (Note 9). The distillation pot residue is a thick oil consisting for the most part of cis-1,5-cyclo-octanediol. An NMR lanthanide shift study showed the alcohol to be 93% (R) and 7% (S), 86% ee, (Note 10 and 11).

2. Notes

1. A 0.5 M THF solution of 9-BBN is available from Aldrich Chemical Company in 800 mL bottles.

2. (+)- α -Pinene (90-92% ee) is available from Aldrich Chemical Company. The pinene was distilled from lithium aluminum hydride before use.

3. Most of the THF is removed by water aspirator vacuum. Excess pinene (0.05 mol, ~8 mL) is removed by applying a 0.05-mm vacuum for 2 hr while warming to 40°C with a water bath. The vacuum should be bled with nitrogen to maintain an inert atmosphere in the reaction flask. Recently Brown's group³ has shown that reduction occurs at an enhanced rate with neat organoborane 1. Excess 1, 1.4 equiv per equiv of 1-octyn-3-one, is used to provide a slight excess of reducing agent to increase the rate for this bimolecular process.

4. B-3-Pinanyl-9-borabicyclo[3.3.1]nonane, 1, is also available from Aldrich Chemical Company under the trade-name, R-Alpine-Borane.

5. 1-Octyn-3-one was obtained by standard Jones oxidation⁴ of racemic 1-octyn-3-ol (in ~80% yield). Racemic 1-octyn-3-ol is available from Aldrich Chemical Company. It is essential to check the ketone for unreacted starting alcohol since racemic alcohol will contaminate the final, optically-active product.

6. GLC can be used to monitor the disappearance of the acetylenic ketone. 1-Octyn-3-one is eluted just after α -pinene from a SE-30 6 ft column at 80°C. The checkers followed the disappearance of ketone by TLC (15% ethyl acetate in hexane).

7. This is the most convenient stage to remove α -pinene since α -pinene and 1-octyn-3-ol have similar boiling points, making separation by distillation difficult. Application of a 0.05-mm vacuum while the flask is warmed to 40°C for several hours will remove most of the α -pinene (0.4 mol, ~ 63.5 mL). Because of the volume of α -pinene, cold traps in the vacuum system may become plugged; therefore the traps will have to be emptied several times. This provides a convenient method to recover liberated (+)- α -pinene.

8. Hydrogen peroxide oxidation of organoboranes is exothermic. Careful, dropwise addition of 30% hydrogen peroxide to the organoborane will provide sufficient heating to maintain a reaction temperature in the 40-50°C range.

9. 1-Octyn-3-ol has the following properties: bp 60-65°C (3.0 mm); IR (neat) cm^{-1} : 3315, 2950, 2860, 2120, 1475, 1380, 1120, 1060, 1025, 650; ^1H NMR (CDCl_3) δ : 0.86 (t, 3 H, $J = 6.6$, CH_3), 1.3-1.4 (m, 6 H), 1.65 (m, 2 H), 2.42 (d, 1 H, $J = 2$, $\text{C}\equiv\text{C-H}$), 3.0 variable (broad, 1 H, OH), 4.33 (m, 1 H); ^{13}C NMR (CDCl_3) δ : 72.6 (C-1), 85.1 (C-2), 62 (C-3), 37.4 (C-4), 31.3 (C-5), 24.6 (C-6), 22.4 (C-7), 13.9 (C-8); $[\alpha]_D^{25} +7.50^\circ$ (neat, density 0.864 g/mL). It has been shown that optical rotation is an unreliable criterion of enantiomer purity of 1-octyn-3-ol.⁵

10. Commercially available $\text{Eu}(\text{hfc})_3$, tris [3-(heptafluoropropyl)hydroxy-methylene)-d-camphorato]europium III, NMR shift reagent, was used as received from Aldrich Chemical Company. The proton on the chiral carbinol carbon was shifted downfield to ~ 11 ppm in CDCl_3 . The R isomer was shifted ~ 0.5 ppm further downfield than the S isomer.

11. Optically pure (+)-1-octyn-3-ol may be obtained by recrystallization of the half acid phthalate with (+)- α -methylbenzylamine (Aldrich Chemical Company). The half acid phthalate salt is made by heating equal molar amounts of 1-octyn-3-ol and phthalic anhydride. This half acid phthalate derivative

is a waxy solid which does not lend itself to recrystallization. Attempts to form crystalline salts of the phthalate derivative with achiral alkyl amines only lead to waxy solids or thick oils. The phthalic amine salt made with racemic 1-octyn-3-ol requires 3-4 recrystallizations from methylene chloride to resolve enantiomers.⁶ The first recrystallization may take several days, with successive recrystallizations becoming easier. If the 86% ee 1-octyn-3-ol is used to make the phthalic amine salt only one facile recrystallization is needed to provide optically-pure alcohol. The pure amine salt melts at 132-134°C. The enantiomeric purity of the salt may be determined by NMR by observing the ethynyl hydrogen doublets at δ 2.48 (minor) and 2.52 (major) (CDCl_3 solvent).

3. Discussion

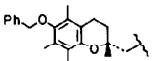
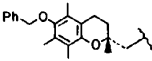
In this procedure, we describe a general method for the synthesis of alkynyl alcohols of high enantiomeric purity. The one-pot asymmetric reduction of 1-octyn-3-one with B-3-pinanyl-9-borabicyclo[3.3.1]nonane provides a mild and efficient method for the preparation of optically active 1-octyn-3-ol. The reduction occurs in good chemical yield and is virtually (>95%) stereospecific (correcting for the use of 90% ee α -pinene). The availability of optically pure α -pinene is a limiting factor in this method, but recently Brown's group has developed a process that provides enantiomerically pure α -pinene.⁷ The reduction can be applied to prepare both enantiomers of 1-octyn-3-ol, since both enantiomers of α -pinene are commercially available; although commercial (-)- α -pinene is only 81.3% ee,⁷ (-)- α -pinene of 92% ee is easily obtained by isomerizing commercial (-)- β -pinene (92% ee).⁸ (Reducing agent 1, made with (-)- α -pinene, will provide (-)-S-1-octyn-3-ol). The α -pinene

liberated (by β -hydride elimination) in the reduction may be recycled without loss of optical purity. Another attractive feature of this reduction is that organoborane **1** is a mild reagent and generally does not affect other functional groups present within the acetylenic ketone. For base sensitive systems that cannot tolerate the standard sodium hydroxide-hydrogen peroxide oxidation an alternative work-up using ethanolamine is available.⁹ Table I illustrates the application of this reduction to other propargyl ketones.⁹ In these cases, tetrahydrofuran was not removed prior to reduction. Removal of tetrahydrofuran provides a faster reaction and slightly higher optical purity.³

The most popular methods of preparing optically active 1-octyn-3-ol involve asymmetric reduction of 1-octyn-3-one with optically-active alcohol complexes of lithium aluminum hydride or aluminum hydride.¹⁰ These methods give optical purities and chemical yields similar to the method reported above. A disadvantage of these metal-hydride methods is that some require exotic chiral alcohols that are not readily available in both enantiomeric forms. Other methods include optical resolution of the racemic propargyl alcohol (100% ee)⁶ (and Note 11) and microbial asymmetric hydrolysis of the propargyl acetates (~15% ee for 1-heptyn-3-ol).¹¹

TABLE I

Reductions of alkynyl ketones with
B-(3)- α -pinanyl-9-BBN

Ketone $\text{RCOC}\equiv\text{CR}'$		Yield (%) ^a	Enantiomeric excess (%) ^b
R	R'		
Ph	Bu	72	85 ^c
Me	Ph	98	72(78)
Pr	C ₆ H ₁₃	68	77 ^c
2-Pr	H	78	91(99)
	Me	77	85:15 ^d
	H	75	91:9 ^d
Me	COOEt	59	71(77)
C ₅ H ₁₁	COOEt	72	85(92)
Ph	COOEt	64	92(100)
t-Bu	Me	0	
Me	t-Bu	62	73 ^c

Isolated yield based on starting ketone. ^bDetermined by analysis of the u(dcm)_3 shifted NMR spectrum. The numbers in parentheses are corrected for 12% ee α -pinene. ^c100% optically pure (+)- α -pinene was used. ^dDiastereomeric ratio (R,R to R,S) determined by LC or NMR analysis of the mixture.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

B-3-Pinanyl-9-borabicyclo[3.3.1]nonane: 9-Borabicyclo[3.3.1]nonane,

9-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)- (10); (73624-47-2)

(R)-(+)-1-Octyn-3-ol: 1-Octyn-3-ol, (R)-(+)- (8); 1-Octyn-3-ol, (R)- (9); (32556-70-0)

9-Borabicyclo[3.3.1]nonane (8,9); (280-64-8)

(+)- α -Pinene: 2-Pinene, (1R,5R)-(+)- (8); Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (R)- (9); (7785-70-8)

1-Octyn-3-one (8,9); (27593-19-7)

Propionaldehyde (8); Propanal (9); (123-38-6)

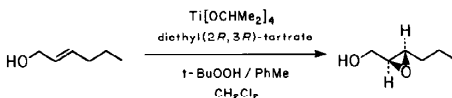
Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium III:

Europium, tris[3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-onato-0,0']- (9); (34788-82-4)

ENANTIOSELECTIVE EPOXIDATION OF ALLYLIC ALCOHOLS:

(2S,3S)-3-PROPYLOXIRANEMETHANOL

(Oxiranemethanol, 3-Propyl-, (2S,3S)-)



Submitted by J. Gordon Hill,¹ K. Barry Sharpless,¹

Christopher M. Exon,² and Ronald Regenye.²

Checked by Mark H. Norman and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer with Teflon blades, thermometer, and nitrogen inlet is charged with 1.00 L of methylene chloride (Note 1) and 39.9 mL (38.1 g, 0.134 mol) of titanium(IV) isopropoxide (Note 2). The flask content is stirred and cooled under nitrogen in a dry ice-ethanol bath to -70°C . To the flask is then added 33.1 g (27.5 mL, 0.161 mol) of diethyl (2*R*,3*R*)-tartrate (Note 3) and 25.0 g (0.25 mol) of E-2-hexen-1-ol (Note 4). A small volume of methylene chloride is used to ensure complete transfer of each material to the reaction flask. To the flask is then added 184.5 mL (0.50 mol) of 2.71 M anhydrous tert-butyl hydroperoxide in toluene (Note 5) which has been precooled to -20°C (Note 6). The addition causes a temperature increase to -60°C ; the temperature of the reaction mixture is allowed to come to 0°C over a 2.0-hr period (Note 7).

A 4-L beaker equipped with a magnetic stirring bar and thermometer is charged with a solution of 125 g of ferrous sulfate and 50 g of tartaric acid in a total volume of 500 mL of deionized water. The solution is stirred and cooled by means of an ice-water bath to 10°C. When the epoxidation reaction mixture reaches 0°C, it is immediately (Note 8) poured into the stirred contents of the beaker. The resulting reaction is mildly exothermic, causing a temperature rise to ca. 20°C (Note 9). After the exothermic reaction has subsided and the temperature has begun to drop (ca. 5 min), the cooling bath is removed and the mixture is stirred at ambient temperature for 30 min. The contents of the beaker are transferred to a 2-L separatory funnel and the aqueous phase is separated and extracted with two 250-mL portions of ether. The combined organic layers are dried over sodium sulfate and filtered. The solvent is removed with a rotary evaporator at 35°C (70 mm) to give 85.9-89.9 g (Note 10) of pale amber oil.

A 2-L, three-necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer with Teflon blades is charged with a solution of the reaction product in 750 mL of ether. The contents of the flask are cooled in an ice-water bath to 3°C. To the flask is added a precooled (3°C) solution of 20 g (0.50 mol) of sodium hydroxide in 500 mL of brine (Note 11). The two-phase mixture is stirred vigorously for 1 hr with continued cooling (Note 12) and then is transferred to a separatory funnel. The aqueous phase is separated and extracted with two 150-mL portions of ether (Notes 13, 14). The combined organic solution (Note 15) is dried over sodium sulfate and filtered. Solvent removal with a rotary evaporator at 35°C (70 mm) followed by concentration with the rotary evaporator at 35°C (12 mm) for 1.0 hr gives 24.7-25.0 g of crude (2S,3S)-3-propyloxiranemethanol as a pale amber oil (Note 16).

The crude product is distilled through a 10-cm Vigreux column (the receiving flask is cooled in an ice-water bath) to yield 22.45-22.84 g (80-81%) of (2S,3S)-3-propyloxiranemethanol as a colorless liquid, bp 31-33°C (0.30-0.40 mm). Analysis by GC indicates a chemical purity of 89-93% (Note 17). The material is fractionally distilled through a 20-cm vacuum-jacketed Vigreux column to obtain 17.69-19.44 g (63-69%), $[\alpha]_D^{22}$ -38.1 to -38.6° (neat), $[\alpha]_D^{23}$ -46.2 to -48.6° (CHCl₃, c 1.0) of a colorless liquid. Analysis by GC indicates a chemical purity of 96-98% (Note 17). An enantiomeric purity of 96.4-97.5% is determined by ¹H NMR analysis of the derived acetate using Eu(hfc)₃, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium-[III], (Note 18) as the chiral shift reagent (Note 19). The enantiomeric purity may also be determined by GC analysis (Note 20) of the derived α-methoxy-α-(trifluoromethyl)phenylacetic acid esters³ (Notes 21, 22). An alternative to the distillation method is purification by preparative HPLC (Notes 23, 24), and bulb-to-bulb distillation (Note 25) to give 21.85 g (78%) of (2S,3S)-3-propyloxiranemethanol as a white solid, mp 19°C, $[\alpha]_D^{25}$ -46.6° (CHCl₃, c 1.0). Analysis by GC of material purified in this manner indicates a chemical purity of >99% (Note 14) and an enantiomeric purity of 96.8% (Notes 20, 21, 22).

2. Notes

1. Fisher Scientific Company methylene chloride, certified ACS grade containing 0.02% water was used; a fresh bottle was used for each run.

2. Titanium(IV) isopropoxide is available from the Aldrich Chemical Company, Inc.

3. (+)-Diethyl L-tartrate was obtained from the Aldrich Chemical Company, Inc.

4. trans-2-Hexen-1-ol was obtained from Alfa Products, Morton/Thiokol, Inc. Analysis by GC (Hewlett-Packard HP 5710A; 50 m x 0.25 mm capillary column or bonded CPS-2 on fused silica; 120°C isothermal) with appropriate standards indicated an E-2-hexen-1-ol content of 96.1% with 0.9% Z-2-hexen-1-ol and 2.9% hexanol as impurities. trans-2-Hexen-1-ol from the Aldrich Chemical Company, Inc. could also be used. This material was of similar composition: 95.4% E-2-hexen-1-ol, 0.8% Z-2-hexen-1-ol and 3.2% hexanol.

5. Anhydrous tert-butyl hydroperoxide in toluene⁴ was prepared starting with Aldrich Chemical Company, Inc. 70% aqueous tert-butyl hydroperoxide. A 500-g lot of this material was swirled in a separatory funnel with 1.0 L of toluene. The aqueous phase was removed and discarded. The organic solution was heated at reflux under nitrogen for 4 hr in a flask equipped with a Dean-Stark trap for water separation (for greater detail see reference 4). The solution was cooled and stored under nitrogen at -20°C (Note 6). The content of tert-butyl hydroperoxide was determined by ¹H NMR according to the equation:

$$\text{Molarity} = \frac{X}{0.1X + 0.32Y}$$

X = integration of tert-butyl resonance
Y = integration of methyl resonance

6. Storage of the solution at -20°C is not necessary.⁴ It does, however, provide a convenient method of precooling the material.

7. Addition of dry ice to the cooling bath was stopped. If the rate of temperature increase was too slow, the ethanol bath was lowered.

8. If the mixture is allowed to stand at 0°C or to warm above this temperature, undesired by-products (TLC) are formed.

9. The temperature should be kept ≤20°C. In some cases, the addition of small amounts of ice to the reaction is necessary.

10. This weight can vary substantially, depending upon the extent to which the solvents, especially toluene, have been stripped from the solution. Concentration need only be carried out until the weight is <100 g.

11. This mixture is prepared by dissolving the sodium hydroxide in the brine at ambient temperature and then cooling the total to 3°C. The resultant cloudy, supersaturated suspension is used in toto. The use of this reagent ensures complete extraction (vide infra) of the somewhat water-soluble product. In addition, it minimizes contact of this material with the aqueous base, conditions which can lead to the Payne rearrangement.⁵

12. Saponification serves to remove the diethyl tartrate as well as to liberate any product which has been transesterified to form a tartrate ester.

13. GC analysis (Note 14) of a third extract showed no product.

14. GC analysis was performed on a column with the following properties: Hewlett-Packard HP 5702A, 2 m x 1/4" OV-101 column, programmed 70-200°C at 8°C/min.

15. GC analysis (Note 14) shows no diethyl (2R,3R)-tartrate, indicating that the saponification was complete.

16. Material of this quality is suitable for many synthetic purposes.

17. The properties of the column are as follows: Hewlett-Packard HP 5790A, 12 m x 0.2 mm cross-linked methyl silicone (fast analysis) column, programmed from 35 to 140°C at 3°C/min.

18. The shift reagent was obtained from the Aldrich Chemical Company, Inc. Drying the $\text{Eu}(\text{hfc})_3$ overnight with a drying pistol at 56°C (refluxing acetone) under vacuum afforded optimum results.

19. The analytical sample of the acetate derivative is prepared as follows. Into a 5-mL, round-bottomed flask equipped with a magnetic stirring bar are placed 2 drops of the reaction product, 15 drops of acetic anhydride,

and 32 drops of pyridine. The solution is stirred at ambient temperature for 2 hr, and the mixture is then transferred to a separatory funnel with the aid of 10 mL of methylene chloride. The methylene chloride solution is washed with two 10-mL portions of 1 M phosphoric acid, the organic layer is dried over MgSO_4 , and the filtered solution is concentrated with a rotary evaporator to give approximately 20 mg of acetate as a colorless oil.

A 5- μL sample of this crude acetate is dissolved in 0.5 mL of benzene- d_6 and transferred to an NMR tube. A solution of 75 mg of $\text{Eu}(\text{hfc})_3$ in 0.5 mL of benzene- d_6 is prepared. A 50- μL portion of the shift reagent solution is added to the acetate sample, the mixture is shaken well, and the ^1H NMR spectrum is recorded. Additional portions of shift reagent are added in 10- μL portions until the acetate methyl resonance (originally at $\delta = 1.65$ ppm) shifts downfield to the region 2.3-3.1 ppm and shows baseline resolution of the resonances from the two enantiomers. A total of 50-90 μL of the shift reagent solution should be required to achieve the desired shift, at which point a chemical shift difference of about 0.2 ppm should be obtained. The %ee is obtained by integration of the two acetate peaks.

20. The column had the following properties: Hewlett-Packard HP 5710A, 50 m x 0.25 mm capillary column of OV-17 (bonded) on fused silica; 175°C isothermal.

21. The analytical sample of α -methoxy- α -(trifluoromethyl)phenylacetic acid ester is prepared as follows. Into a 5-mL, capped, amber vial equipped with a magnetic stirring bar are placed 20 mg of the reaction product, 1.0 mL of methylene chloride, 87 mg of (+)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (Note 22), 4 drops of triethylamine and 1 crystal of 4-dimethylaminopyridine. The mixture is stirred at ambient temperature for 1.5 hr, at which point TLC (Note 26) indicates complete conversion to the ester.

Addition of 4 drops of N,N-dimethyl-1,3-propanediamine and concentration on a rotary evaporator at 35°C (70 mm) affords a yellow oil. This material is filtered through 10 g of E. Merck silica gel 60 (70-230 mesh) with 9:1 hexanes-ethyl acetate until TLC analysis indicates no further product elution. The total eluate is concentrated on a rotary evaporator at 35°C (70 mm). The resultant colorless oil is subjected to GC analysis.

A sample of E-2-hexen-1-ol in methylene chloride was epoxidized at 20°C with m-chloroperoxybenzoic acid. The resultant racemic epoxy alcohol, upon conversion to the diastereomeric (+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid esters in the manner described above, provided a GC standard for determination of the enantiomeric excess obtained in the asymmetric epoxidation.

22. The acid chloride was prepared³ from (+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid which was used as obtained from Aldrich Chemical Company, Inc.

23. Purification by preparative HPLC is accomplished as follows. The crude product is taken up in 60 mL of 4:1 hexanes-ethyl acetate. The solution is subjected to preparative HPLC (Note 24) using the same solvent system. Chromatography is monitored by TLC (Note 26) and the appropriate fractions are combined. Solvent removal with a rotary evaporator at 35°C (12 mm) gives a colorless oil. This material is subjected to bulb-to-bulb distillation at 75-90°C (8 mm).

24. A Waters Associates Prep LC/System 500 with two cartridges (1.0 kg) of PrepPak-500/Silica was used. The course of the chromatography was followed with a refractive index detector. Approximately 3.6 L of solvent was eluted prior to the product band.

25. A Kugelrohr apparatus purchased from the Aldrich Chemical Company, Inc., was used. The receiving bulb was cooled with an ice-water bath. The temperature indicated is the oven temperature.

26. E. Merck silica gel F-254 plates were used, with 2:1 hexanes-ethyl acetate as eluent. Visualization was effected by spraying with a 10% phosphomolybdic acid in ethanol solution followed by heating with a hot air gun. (2S,3S)-3-Propyloxiranemethanol had an R_f of ca. 0.3.

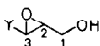
3. Discussion

Both the synthetic^{6a} and mechanistic^{6b} aspects of this asymmetric epoxidation process have been reviewed recently. While the process has great scope regarding the allylic alcohol substrate, there are two classes of substrates which present difficulties. These limitations will be best appreciated by reference to the recent reviews;⁶ however, the main problems are worth mentioning here. When difficulties arise, they are almost never due to the failure of the asymmetric epoxidation process itself, but can be traced instead to the nature of the epoxy alcohol product.

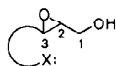
Water-soluble products (e.g., 3- and 4-carbon epoxy alcohols) present obvious isolation problems which have been only partly solved. The other troublesome class of products includes those epoxy alcohols which are unstable under the epoxidation and/or isolation conditions. This latter class consists of the three main types shown below:



1



2



3

Type 1 is sensitive to nucleophilic opening at the primary epoxide carbon (C-3). Type 2 represents cases where the substituent Y facilitates opening at carbon-3 through resonance stabilization of the incipient carbonium ion. Finally, type 3 includes those cases in which the product bears a heteroatom substituent (X) placed so that a five- or six-membered ring results from anchimerically-assisted opening of the epoxide at carbon-3. Not even these structural features (i.e., as in 1, 2, and 3) are always fatal, for some representatives of types 1, 2 and 3 afford good yields of the desired epoxy alcohols.⁶ Furthermore, when the structure of a given case is marginal, we have found that modification of the epoxidation and/or isolation procedures can lead to substantially improved yields. With such sensitive epoxy alcohols, milder isolation procedures are always employed (see ref. 6a and 9 for a discussion of these modified work-up methods). However, certain substrates of types 1, 2 and 3 still fail completely with all current procedures. The best we have been able to do in these difficult cases is to use a strategy which actually takes advantage of the facile epoxide opening process.^{6,7}

Questions are often asked concerning the catalytic nature of the asymmetric epoxidation. One notes that the present procedure calls for 50% catalyst. With very favorable substrates, one can realize complete conversion and >95% ee using as little as 2% catalyst.⁶ In the present case, the reaction stops at about 80% conversion using 2% catalyst, and almost reaches completion with 10% catalysis.⁸ The selection of 50% catalyst is a compromise aimed at making the procedure applicable to a wider range of substrates. In the literature, most applications of asymmetric epoxidation use 100% catalyst. This is rarely necessary, but ensures rapid and complete epoxidation in small scale reactions where cost of the reagents is not an

issue. The cases yielding epoxy alcohols which are sensitive to opening require the most catalyst, because the open-diol products are potent inhibitors of the epoxidation catalysis.^{6a} If one wished to produce molar amounts of a given epoxy alcohol, it would be worthwhile to determine the optimum catalyst loading for the case at hand. In addition to the cost incentive, the isolation procedure becomes simpler as the amount of catalyst is decreased.

The aqueous tartaric acid work-up procedure described here is the simplest method for removing the titanium species, but it should only be used with relatively stable epoxy alcohols which are not water-soluble. In this regard, the six carbon epoxy alcohol made here probably represents the lower limit, as it is on the verge of water solubility. Of course, one cannot assume this work-up will succeed with all six carbon or larger epoxy alcohols, for in addition to limited water solubility, the product must be fairly resistant to acid-catalyzed epoxide opening processes. *For water-soluble and/or acid-sensitive epoxy alcohols, the "sodium sulfate work-up" is generally preferred.*^{6a,9} When making a particularly sensitive epoxy alcohol, one should not only use this sodium sulfate work-up but one should also modify the initial stage of the epoxidation process so that the reaction mixture only warms to -20°C rather than to 0°C.

Finally, two other practical points are worth mentioning. The early procedures for asymmetric epoxidation called for dilute solutions of sodium hydroxide to effect tartrate ester hydrolysis. For the reasons given in Note 11, one should always (unless one is certain that the epoxy alcohol is completely insoluble in water) use instead NaOH in brine. In this procedure, the excess tert-butyl hydroperoxide (TBHP) was destroyed early in the work-up (FeSO_4), although this is not essential because dilute solutions of TBHP are

not dangerous. Other methods for removing excess TBHP in these epoxidations have been reviewed.^{6a} One of the simplest is to remove it as the azeotrope with toluene. We have removed up to 0.5 mol of TBHP by this means.¹⁰

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
2. Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ 07110.
3. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.
4. Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607-3608.
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8. Note, however, that in some cases, lower catalyst levels cause the enantiomeric excess to fall off. For example, the title compound is produced with 90% ee using 10% catalyst and with 97% ee using 50% catalyst.

9. The "sodium sulfate work-up" should be used in place of the "tartaric acid work-up", employed in the present procedure, whenever one is dealing with a water-soluble and/or acid-sensitive epoxy alcohol. The early stages of this alternate work-up are as follows: the reaction mixture is removed from the freezer (ca. -20°C), and, while it is stirred (magnetic or mechanical depending on the scale), ether is added to the cold reaction mixture, followed immediately by a saturated sodium sulfate solution (no cooling bath is used at this stage and the ether is not precooled). We use 1 mL of saturated Na_2SO_4 solution per mmol of $\text{Ti}(\text{O}-i\text{-Pr})_4$ (note this is about 3.3 times more than was recommended in an earlier¹¹ procedure). The volume of ether added should be at least 1 mL per mL of saturated Na_2SO_4 solution used, and more ether is beneficial.

The heterogeneous mixture that results is stirred vigorously for about 2 hr at room temperature. It is then filtered through a Celite pad and the resulting orange-yellow paste is washed with several portions of anhydrous ether until the paste becomes somewhat granular. The orange-yellow layer is scraped off the Celite pad into an Erlenmeyer flask. Ethyl acetate is added along with a magnetic stirring bar and the resulting suspension is stirred vigorously for 5 min in boiling ethyl acetate. The slurry is then filtered through the same Celite pad, and the orange-yellow solid is washed once with hot ethyl acetate. Treatment of the filtrand in this manner is a key improvement *which usually increases the total isolated yield by 10 to 15%*. The combined filtrates are concentrated to afford crude product along with the tartrate diester and any excess TBHP. This material is ready for the next stage of the work-up which involves removal of the tartrate ester. The present preparation describes (vide supra) hydrolysis of the ester with

NaOH/brine. For alternate ways of separating the epoxy alcohols from the tartrate ester see reference 6a (this reference also describes several ways for removing the TBHP).

10. Hill, J. G., unpublished results.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Titanium(IV) isopropoxide: Isopropyl alcohol, titanium(4+) salt (8);

2-Propanol, titanium(4+) salt (9); (546-68-9)

Diethyl (2R,3R)-tartrate: Tartaric acid, diethyl ester, L-(+)- (8);

Butanedioic acid, 2,3-dihydroxy-[R-(R*,R*)]-, diethyl ester (87-91-2)

E-2-Hexen-1-ol: 2-Hexen-1-ol, (E)- (8,9); (928-95-0)

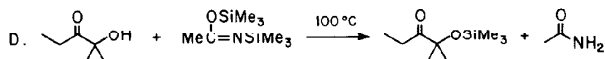
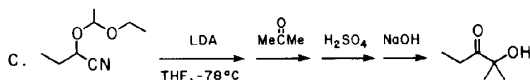
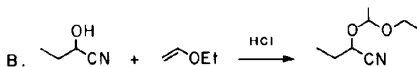
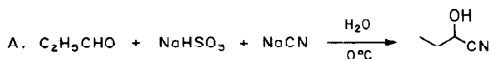
tert-Butyl hydroperoxide (8); Hydroperoxide, 1,1-dimethylethyl (9); (75-91-2)

Tris[3-(heptafluoropropylhydroxymethylene)-d-camphoratoeuropium(III):

Europium, tris[3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,1,1-/-

trimethylbicyclo[2.2.1]heptan-2-onato-0,0']- (9); (34788-82-4)

(3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]-)



Submitted by Steven D. Young, Charles T. Buse, and Clayton H. Heathcock.¹
 Checked by Joseph R. Flisak, Sami Farahat, Stan S. Hall, Hugh W. Thompson,
 and Gabriel Saucy.

1. Procedure

A. *2-Hydroxybutyronitrile*. A 3-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer and thermometer and charged with 312 g (3.0 mol) of sodium bisulfite and 1050 mL of water. The stirrer is started and after the sodium bisulfite has dissolved, the flask is placed in an ice-salt bath. A solution of 147 g (3.0 mol) of sodium cyanide (Note 1) in 450 mL of water and 174 g (3.0 mol) of propionaldehyde (Note 2) are separately cooled to 0°C in ice-salt baths. When the temperature of the vigorously-stirring sodium

bisulfite solution has stabilized at 0°C the cold propionaldehyde is added in one portion. The temperature of the reaction solution immediately increases to ca. 35°C, then returns to ca. 0°C. After 30 min the cold sodium cyanide solution is added in one portion. The reaction mixture again warms to ca. 15°C and then returns to ca. 0°C. This mixture is stirred for 2 hr at 0°C, during which time a thick white precipitate of sodium sulfite forms. The supernatant liquid is decanted into a 4-L separatory funnel and the precipitate is washed with 1 L of ice-water. The combined aqueous solution is extracted with three 1-L portions of ethyl ether. The combined ether extracts are washed with 1 L of saturated brine and dried by stirring (magnetic stirring bar) over magnesium sulfate for 2 hr. The solution is filtered through a coarse, sintered-glass funnel and the ether is removed with a rotary evaporator at water aspirator pressure. After the pH of the residue is adjusted to 5 with a few drops of concentrated hydrochloric acid (Note 3), the residue is distilled to give 154-192 g (60-75%) of 2-hydroxybutyronitrile, bp 108-114°C (30 mm), as a colorless liquid (Note 4).

B. 2-[(1'-Ethoxy)-1-ethoxy]butyronitrile. A 1-L three-necked, round-bottomed flask is equipped with a condenser topped with a calcium chloride drying tube, a magnetic stirring bar, a 500-mL pressure-equalizing addition funnel, and a thermometer. The flask is charged with 174 g (2.05 mol) of 2-hydroxybutyronitrile to which 0.5 mL of concentrated hydrochloric acid has been added. The addition funnel is charged with 221 g (3.07 mol) of ethyl vinyl ether (Note 5), which is then added dropwise to the stirred cyanohydrin at such a rate that the temperature is maintained at ca. 50°C. When the addition is complete, the mixture is heated to 90°C for 4 hr. The condenser is replaced with a distillation head and the dropping funnel and thermometer are replaced with stoppers. Direct distillation of the gold-yellow solution

from the reaction flask yields 226-277 g (70-86%) of nearly pure 2-[(1'-ethoxy)-1-ethoxy]butyronitrile, bp 85-87°C (30 mm), as a colorless liquid (Note 6).

C. 2-Hydroxy-2-methylpentan-3-one. A dry, 5-L three-necked (including a thermometer well), round-bottomed flask is equipped with a mechanical stirrer, low temperature thermometer, nitrogen inlet, rubber septum, and a 1-L, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. The flask is charged with 775 mL of dry tetrahydrofuran (Note 7) and 166 g (1.64 mol) of dry diisopropylamine (Note 8). The contents of the flask are cooled to -10°C (dry ice-acetone bath) and 1095 mL (1.6 mol) of 1.5 M butyllithium in hexane (Note 9), which has been transferred to the addition funnel by means of a 16-gauge cannula and argon pressure, is slowly added to the stirred solution at such a rate as to maintain a temperature of -10°C. After the addition is complete 50 mL of dry THF is added to the addition funnel with a syringe to rinse the walls of the funnel; the rinse is added, and then the mixture is cooled to -75°C. The addition funnel is charged by syringe with 246 g (1.6 mol) of 2-[(1'-ethoxy)-1-ethoxy]butyronitrile, which is then added at such a rate that the temperature does not exceed -70°C. The mixture is stirred for 10 min and 104 g (1.8 mol) of dry acetone (Note 10) is added by syringe over a 30-min period at such a rate that the temperature of the reaction mixture does not exceed -70°C. When the addition is complete the cooling bath is removed and the reaction mixture is allowed to warm to 0°C. The solution is poured into 1 L of water and the resulting mixture is concentrated at aspirator pressure with a rotary evaporator (30°C water bath) to remove the volatile organic compounds. The aqueous residue is extracted with three 1-L portions of methylene chloride. The organic extracts are combined and washed with two 500-mL portions of water, then concentrated with

a rotary evaporator (25°C water bath) at aspirator pressure to obtain a yellow syrupy residue. This material is stirred with 680 mL of methanol and 340 mL of aqueous 5% sulfuric acid overnight at room temperature. The methanol is evaporated with a rotary evaporator (30°C water bath) at aspirator pressure and the yellow residue is extracted with three 1-L portions of ethyl ether. The combined ether extracts are shaken in a 4-L separatory funnel with 210 mL of 10 N aqueous sodium hydroxide for 15 min (Note 11). The layers are separated, and the ether layer is washed with 500 mL of brine and dried by stirring (magnetic stirring bar) over magnesium sulfate for 2 hr. The drying agent is removed by filtration through a coarse sintered-glass funnel and the ether is removed with a rotary evaporator (water bath below 40°C) at aspirator pressure. The yellow-orange liquid residue is distilled to obtain 82-115 g (45-63%) of 2-hydroxy-2-methylpentan-3-one, bp 57-65°C (15 mm), as a pale yellow liquid (Notes 12, 13).

D. *N*-Methyl *N*-trimethylsilylacetamido-2-pentanone. A dry, 500 mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser with a nitrogen inlet, and a thermometer is charged with 84 g (0.72 mol) of 2-hydroxy-2-methylpentan-3-one and 74 g (0.36 mol) of *N*,*O*-bis(trimethylsilyl)acetamide (Note 14). The mixture is heated at 100°C for 12 hr with stirring and then cooled to room temperature, at which point the mixture becomes a semisolid as the acetamide crystallizes. The semisolid mixture is diluted with 50 mL of water and stirred at room temperature for 1 hr (Note 15). After the stirring is stopped, 200 mL of hexane is added and the layers are separated. The aqueous layer is extracted with 100 mL of hexane. The combined hexane extracts are washed with four 100 mL portions of water and then dried over magnesium sulfate for 2 hr. After removal of the drying agent by filtration through a coarse sintered-glass funnel, the hexane

is evaporated with a rotary evaporator (25°C water bath) at aspirator pressure. The crude, pale yellow oil is distilled to afford 105-112 g (75-80%) of 2-methyl-2-trimethylsilyloxypentan-3-one, bp 71-75°C (15 mm), as a colorless liquid (Note 16).

2. Notes

1. *CAUTION! Sodium cyanide and the propionaldehyde cyanohydrin are extremely toxic. Great care should be taken when using these materials. Reactions should be carried out in a well-ventilated hood and suitable protective clothing should be worn at all times.*

2. Propionaldehyde was obtained from Aldrich Chemical Company, and was used without further purification.

3. If HCl is omitted, the cyanohydrin reverts to HCN and propionaldehyde upon attempted distillation. The checkers found it necessary to ensure that the residue was acidic by adjusting the pH to 5 by testing the residue with wet pH paper.

4. The infrared spectrum (neat) shows absorption at 3420, 2960, 2310, and 1460 cm^{-1} .

5. Ethyl vinyl ether was obtained from Aldrich Chemical Company, and was used without further purification.

6. The infrared spectrum (neat) shows absorption at 2970, 1425, and 1385 cm^{-1} . The $\text{C}\equiv\text{N}$ absorption is not observed.

7. Tetrahydrofuran is distilled under a nitrogen atmosphere from sodium/benzophenone immediately prior to use.

8. Diisopropylamine is distilled under a nitrogen atmosphere from calcium hydride prior to use. It may be stored under nitrogen for one week without redistillation.

9. *Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used butyllithium, 1.5 M in hexane from Foote Mineral Company, and measured it by transferring the solution to a 2-L, graduated cylinder stoppered with a rubber septum with a 15-gauge cannula and argon. The solution was then transferred directly to the reaction vessel by the same procedure. The checkers used fresh butyllithium, 1.55 M in hexane under argon, from Aldrich Chemical Company. A reagent bottle was connected in series with the addition funnel by using the cannula, and then about half of the required amount of reagent was transferred using positive argon pressure. After this quantity has been added to the reaction vessel, the rest of the reagent is transferred to the funnel and the addition continued. Stainless steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass, Inc. and Aldrich Chemical Co.

10. ACS Certified acetone was obtained from Fisher Chemical Company, and distilled from 3 Å molecular sieves immediately prior to use.

11. Periodic shaking (once every 3 min) is sufficient to effect cyanohydrin hydrolysis.

12. The ^1H NMR (200 MHz, CDCl_3) spectrum is as follows δ : 1.12 (t, 3 H, $J = 7.2$), 1.39 (s, 6 H), 2.59 (q, 2 H, $J = 7.2$), 3.85 (s, 1 H). The infrared spectrum (neat) shows absorption at 3450, 2960, and 1705 cm^{-1} .

13. In one run, the checkers, at this point obtained 241 g, bp $116\text{--}120^\circ\text{C}$ (12 mm) of the protected cyanohydrin (NMR), which had not been deprotected and hydrolyzed, rather than the expected product. In this case, the entire distillate was resubjected to the acid and base sequence, which afforded the desired product in a 61% overall isolated yield.

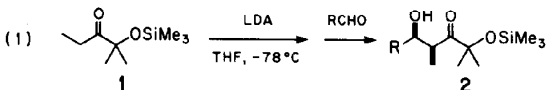
14. N,O-Bis(trimethylsilyl)acetamide was obtained from Aldrich Chemical Company and used without further purification.

15. This process is necessary to insure hydrolysis of any unreacted N,O-bis(trimethylsilyl)acetamide which inevitably contaminates the product if the step is omitted.

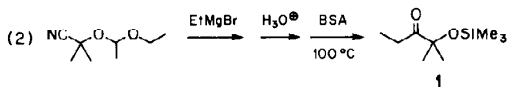
16. The ^1H NMR spectrum (200 MHz, CDCl_3) is as follows δ : 0.15 (s, 9 H), 1.02 (t, 3 H, $J = 7.2$), 1.33 (s, 6 H), 2.67 (q, 2 H, $J = 7.2$). The infrared spectrum (neat) shows absorptions at 2980 and 1720 cm^{-1} .

3. Discussion

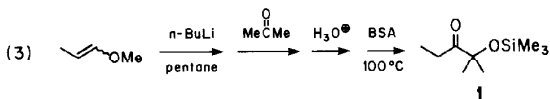
2-Methyl-2-trimethylsilyloxypentan-3-one (**1**) is the prototype member of a series of α -trimethylsilyloxy ketones that are useful for stereoselective aldol addition reactions (eq 1).² β -Hydroxy ketones **2** may be converted into β -hydroxy acids,² β -hydroxy aldehydes,³ and other β -hydroxy ketones.⁴



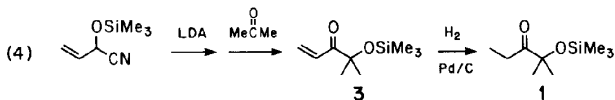
Compound **1** has also been prepared by the following methods. Addition of ethylmagnesium bromide to the protected cyanohydrin of acetone, followed by hydrolysis and silylation provides **1** in 40% yield (eq 2).² Metallation of 1-methoxypropene by butyllithium in pentane⁵ gives 1-lithio-1-methoxypropene, which reacts with acetone to give, after hydrolysis and silylation, ketone **1**



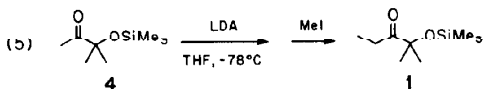
in 25-30% overall yield (eq 3).⁶ The trimethylsilyl ether of acrolein



cyanohydrin, prepared by the method of Hünig,⁷ may be metallated and added to acetone to provide an enone which is hydrogenated to 1 (eq 4).⁸ Although the



overall yield in this sequence can be quite high, the intermediate enone 3 polymerizes very readily, and the procedure is not reliable on a large scale. Compound 1 has also been prepared by methylation of the lithium enolate of the lower homolog, 4, (eq 5).⁹ Although this alkylation provides



1 in 60% yield on a 2-mmol scale, the desired product is accompanied by a significant quantity of the dimethylated product, from which it is not easily separated.⁸

1. Department of Chemistry, University of California, Berkeley, CA 94720.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Methyl-2-trimethylsilyloxypentan-3-one: 3-Pentanone,
2-methyl-2-[(trimethylsilyl)oxy]- (9); (72507-50-7)
2-Hydroxybutyronitrile: Butyronitrile, 2-hydroxy- (8); Butanenitrile,
2-hydroxy- (9); (4476-02-2)
Propionaldehyde (8); Propanal (9); (123-38-6)

2-[(1'-Ethoxy)-1-ethoxy]butyronitrile: Butanenitrile, 2-(1-ethoxyethoxy)-, (R*,R*)- or (R*,S*)- (9); (72658-42-5) or (72658-43-6), respectively

Ethyl vinyl ether: Ether, ethyl vinyl (8); Ethene, ethoxy- (9); (109-92-2)

2-Hydroxy-2-methylpentan-3-one: 3-Pentanone, 2-hydroxy-2-methyl- (8,9); (2834-17-5)

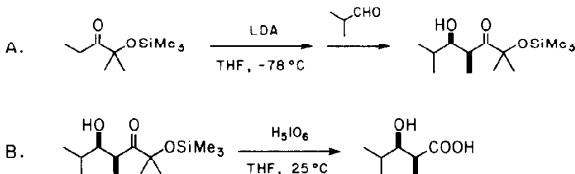
Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

N,O-Bis(trimethylsilyl)acetamide: Acetamidic acid, N-(trimethylsilyl)-, trimethylsilyl ester (8); Ethanimidic acid, N-(trimethylsilyl)-, trimethylsilyl ester (9); (10416-59-8)

(2S,3R)-2,4-DIMETHYL-3-HYDROXPENTANOIC ACID

(Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,S*)-(±)-)



Submitted by B. Bal, C. T. Buse, K. Smith, and Clayton H. Heathcock.¹

Checked by Joseph R. Flisak, Stan S. Hall, Hugh W. Thompson,
and Gabriel Saucy.

1. Procedure

A. *5-Hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one*. A dry, 1-L, four-necked (including a thermometer well), round-bottomed flask equipped with an efficient mechanical stirrer, thermometer, graduated 250-mL pressure-equalizing addition funnel sealed with a rubber septum, and a nitrogen inlet is charged with 125 mL of dry tetrahydrofuran (Note 1) and 31 mL (0.22 mol) of diisopropylamine (Note 2). The stirrer is started and 137 mL (0.20 mol) of 1.5 M butyllithium in hexane is transferred to the addition funnel by means of a 16-gauge cannula and argon pressure (Note 3). The reaction flask and its contents are cooled to below -5°C by immersion in a dry ice-acetone bath that is maintained at -10 to -15°C by the occasional addition of dry ice. The butyllithium is added dropwise over a period of 20 min. After the addition is

complete 10 mL of dry tetrahydrofuran is added to the addition funnel with a syringe to rinse the walls of the funnel and the rinse is then added to the pale yellow solution. After the addition is complete the solution is stirred for an additional 15 min, and is then cooled to below -70°C (dry ice-acetone bath). While the reaction solution is cooling, a solution of 37.7 g (0.20 mol) of 2-methyl-2-trimethylsilyloxypentan-3-one (Note 4) in 10 mL of dry tetrahydrofuran is introduced through the septum into the addition funnel. When the lithium diisopropylamide (LDA) solution has cooled to below -70°C the ketone is slowly added to the solution over a period of 20-25 min to ensure that the reaction temperature is maintained below -70°C . After the addition is complete 10 mL of dry tetrahydrofuran is added to rinse the walls of the addition funnel, the rinse is added, and the stirred reaction solution is maintained below -70°C for an additional 30-40 min. During this time the addition funnel is charged through the septum with a solution of 14.4 g (0.20 mol) of isobutyraldehyde (Note 5) in 10 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirring yellow enolate solution at -70°C over a 15-min period and then the addition funnel is again rinsed with 10 mL of dry tetrahydrofuran, and the rinse added to the reaction mixture. After 10-15 min 200 mL of a saturated aqueous ammonium chloride solution is added to the vigorously stirred, -70°C reaction mixture. At this point stirring is discontinued, the cooling bath is removed and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a 2-L separatory funnel, 200 mL of ether is added to the flask and the ether rinse is then transferred to the separatory funnel. The layers are shaken, then separated, and the aqueous phase is extracted again with 200 mL of ether. The combined organic phase is washed with 200 mL of water and 200 mL of saturated brine and then dried over

magnesium sulfate. After removal of the drying agent by filtration the solvents are removed with a rotary evaporator at aspirator pressure to give 52.1-52.4 g of a pale yellow oil that is a 63:37 mixture of the expected product and the starting material. Most of the starting material is then selectively removed by stirring (magnetic stirring bar) at 25°C at reduced pressure (vacuum pump, 0.1-0.08 mm) for 19 hr to yield 35.2 g of a 90:10 mixture (31.7 g, 61%), which is used without further purification for Part B (Notes 6 and 7).

B. (2*SR*,3*RS*)-2,4-Dimethyl-3-hydroxypentanoic Acid. A dry, 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a nitrogen inlet is flushed with nitrogen, charged with 12.5 g (55 mmol) of periodic acid (Note 8) and 150 mL of dry tetrahydrofuran (Note 1), and then sealed with a stoppered, 25-mL, pressure-equalizing addition funnel. The solution is stirred vigorously and cooled to 0-5°C with an ice-salt bath. During this time the addition funnel is charged with a solution of 12.0 g of 5-hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one (10.8 g, 41 mmol of ketone from a 90:10 mixture from Part A) in 10 mL of dry tetrahydrofuran, which is then rapidly introduced (1 min) to the cold, stirred solution. After the addition is complete 5 mL of dry tetrahydrofuran is added to the addition funnel to rinse the walls of the funnel and this rinse is then added to the reaction solution. The cooling bath is removed after 15 min and stirring is continued for 1.5 hr, during which time a white precipitate forms. In the meantime, 52 g (0.5 mol) of sodium bisulfite is mixed with 100 mL of distilled water in a 500-mL filtering flask with a side hose connection and cooled to 0-5°C with an ice-salt bath. The reaction mixture is filtered directly through filter paper with suction into the cold slurry of sodium bisulfite. The residue is rinsed with 50 mL of dry ether (Note 9), which is

added to the filter funnel and drawn by suction into the yellow solution. After magnetic stirring of the cold mixture for 20 min the contents of the flask are introduced into a 500-mL separatory funnel and the layers are separated. The aqueous layer (pH 4.3) is extracted twice with 100 mL of ether and the combined yellow organic layer is washed with 125 mL of distilled water and separated (the pH of the wash is 2.6-3.5). The organic layer is dried over magnesium sulfate for 1 hr, filtered to remove the drying agent, and the solvents are removed with a rotary evaporator at aspirator pressure. Distillation of the dark yellow oil affords 4.9-5.4 g (82-89%) of (2SR,3RS)-2,4-dimethyl-3-hydroxypentanoic acid, bp 85-89°C (0.01 mm), as a viscous, yellow-green liquid (Note 10). Crystallization from hexane using decolorizing carbon provides 4.6-5.0 g (77-83%) of pure hydroxy acid, mp 75-76°C, as white crystals (Note 11).

2. Notes

1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium/benzophenone immediately prior to use.

2. Diisopropylamine was distilled, bp 85°C, under a nitrogen atmosphere from calcium hydride immediately prior to use.

3. *Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used fresh butyllithium from Foote Mineral Company, Johnsonville, Tennessee. The checkers used fresh butyllithium, 1.6 M in hexane under argon, from Aldrich Chemical Company, Inc. The butyllithium solutions may be standardized;² however, both the submitters and the checkers chose to use fresh reagents and forego the titration. Stainless

steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass Inc. and Aldrich Chemical Company, Inc.

4. 2-Methyl-2-trimethylsilyloxypentan-3-one was prepared by the method of Young, Buse and Heathcock, *Org. Synth.*, preceding article, this volume.

5. Isobutyraldehyde was freshly distilled, bp 64-65°C.

6. The submitters report that the starting material can be removed within 4 hr to give 38-42 g of the 90:10 mixture if the concentration is continued with the rotary evaporator rather than a stationary flask at 0.5-0.1 mm.

7. The ^1H NMR (200 MHz, CDCl_3) spectrum of the product (taken from a spectrum of a 90:10 mixture) is as follows δ : 0.18 (s, 9 H), 0.89 (d, 3 H, $J = 6.7$), 1.02 (d, 3 H, $J = 6.5$), 1.08 (d, 3 H, $J = 7.1$), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.68 (d of septets, 1 H, $J = 8.4$ and 6.6), 2.95 (d, 1 H, $J = 2.6$, OH), 3.42 (dt, 1 H, $J = 8.5$, 2.6, and 2.6), 3.59 (dq, 1 H, $J = 7.0$ and 2.6). The infrared spectrum (film) of a 93:7 mixture shows absorptions at 1700 and 3600-3300 cm^{-1} .

8. Fresh periodic acid was obtained from Aldrich Chemical Company, Inc. and stored in a desiccator.

9. Reagent grade diethyl ether from a freshly opened container was used without further drying.

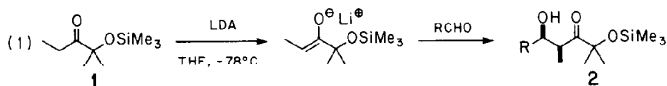
10. The checkers discovered that the desired hydroxy acid is sensitive to strong acid and heat. Early runs of Part B by the checkers using the original conditions recommended by the submitters involved stirring the bisulfite slurry at room temperature for 3-4 hr, simple partitioning without an aqueous backwash and drying of the bisulfite oxidation mixture, and distillation of the product at 0.8 mm reduced pressure. These runs consistently resulted in acid-catalyzed transformation, either in the workup

or in distillation, and led to mixtures contaminated with isobutyraldehyde produced by a retroaldol reaction, as well as with other unsaturated materials. Distillation of one of these runs, which had used a crude 58:42 mixture from Part A as starting material, afforded 13.4 g (53%) of α,γ,γ -trimethylbutyrolactone, bp 85-105°C (0.8 mm), as a yellow-green liquid by dehydration-lactonization. Crystallization from hexane provided 10.1 g (40%) of pure lactone, mp 50-51°C, as white crystals. The lactone had the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 1.28 (d, 3 H, $J = 7.1$), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.71 (superficial t, 1 H, $J = \text{ca. } 12$), 2.30 (dd, 1 H, $J = 12.6$ and 8.9), 2.83 (16-line m; 1 H, $J = 11.2, 8.9$, and 7.1); ^{13}C NMR (50 MHz, CDCl_3) δ : 15.6, 27.0, 29.0, 35.6, 43.5, 81.8, 179.1; IR (CCl_4) cm^{-1} : 1780; Mass spectrum, m/z (rel intensity): 129 ($\text{M}^+ + 1$, 1), 113 (33), 84 (16), 69 (30), 59 (34), 43 (100).

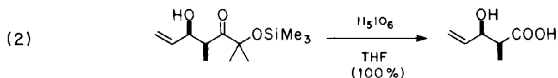
11. The hydroxy acid showed the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 0.89 (d, 3 H, $J = 6.6$), 1.02 (d, 3 H, $J = 6.6$), 1.21 (d, 3 H, $J = 7.1$), 1.71 (octet, 1 H, $J = 6.7$), 2.71 (dq, 1 H, $J = 7.3$ and 3.4), 3.64 (dd, 1 H, $J = 8.1$ and 3.4), 6.7 (br s, 2 H, OH and CO_2H); IR (CCl_4) cm^{-1} : 1700, 3600-2500.

3. Discussion

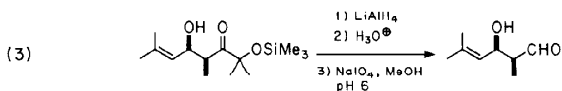
The stereochemistry of the aldol addition reaction has been actively investigated in recent years and several methods for achieving high stereoselectivity have been developed.³ One of these utilizes the preformed lithium enolates of compounds such as 1.⁴ Compound 1 gives a single enolate, which has the *Z* configuration. This enolate reacts with aldehydes to give β -hydroxy ketones (2) with high stereoselectivity (eq 1).



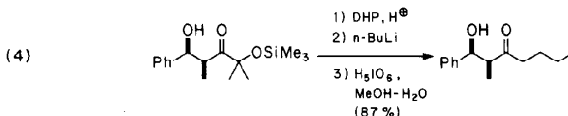
Compounds 2 may be directly cleaved with periodic acid to obtain β-hydroxy acids (e.g., eq 2).^{4,5}



Alternatively, the carbonyl group may be reduced, the silyl group hydrolyzed, and the resulting vicinal diol cleaved with buffered sodium periodate to obtain the β-hydroxy aldehyde (e.g., eq 3).^{6,7}









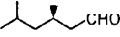



Finally, the hydroxy group may be protected as the tetrahydropyranyl ether, an aryl or alkyl lithium reagent added to the carbonyl, and the resulting vicinal diol cleaved to obtain the corresponding β-hydroxy ketone (e.g., eq 4).⁸



Selected examples of the addition of ketone 1 to a variety of aldehydes are collected in Table I.

TABLE I
CONDENSATION OF KETONE 1 WITH ALDEHYDES (eq 1)

Aldehyde	β -Hydroxy Yield (%)	Ketone mp	β -Hydroxy Yield (%)	Acid mp	Ref.
	80	oil	100	oil	5
	98	oil	62	oil	9
	96	oil	97	oil	10
	43	oil	—	—	7
	93	oil	61	73-75°C	4
	51	oil	76	119-120°C	4
	78	oil	87	oil	4
	100 ^a	oil	65	134-135°C ^d	4
	61 ^b	oil	—	—	7
	75 ^c	oil	—	—	6

a. This is a 4:1 mixture of Cram: anti-Cram isomers.

b. Major isomer.

c. This is a 15:1 mixture of Cram: anti-Cram isomers.

d. This is a 1.3:1 mixture of Cram: anti-Cram isomers.

1. Department of Chemistry, University of California, Berkeley, CA 94720.
2. (a) Jones, R. G.; Gilman, H. In "Organic Reactions", Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, p. 353; (b) Kofron, W. G.; Baclawski, L. *M. J. Org. Chem.* **1976**, *41*, 1879.
3. (a) Heathcock, C. H. In "Comprehensive Carbanion Chemistry", Durst, T.; Buncl, E., Eds.; Elsevier: New York, 1984; Vol. II; (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In "Topics in Stereochemistry", Eliel, E. L.; Allinger, N. L.; Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13; (c) Heathcock, C. H. In "Asymmetric Synthesis", Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3.
4. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe J. *J. Org. Chem.* **1980**, *45*, 1066.
5. Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825.
6. Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.
7. Heathcock, C. H.; Young, S. D., unpublished results.
8. White, C. T.; Heathcock, C. H. *J. Org. Chem.* **1981**, *46*, 191.
9. Heathcock, C.H.; Maxwell, B., unpublished results.
10. Heathcock, C. H.; Finkelstein, B., unpublished results.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic acid: Pentanoic acid, 3-hydroxy-2,4-dimethyl-(R*,S*)-(±)- (9); (64869-26-7)

5-Hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one: 3-Heptanone, 5-hydroxy-2,4,6-trimethyl-2-[(trimethylsilyloxy)]-, (R*,S*)-(±)- (9); (64869-24-5)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

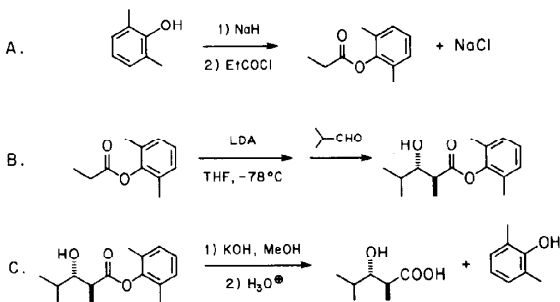
Butyllithium: Lithium, butyl- (8,9); (109-72-8)

2-Methyl-2-trimethylsilyloxypentan-3-one: 3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]- (9); (72507-50-7)

Isobutyraldehyde (8); Propanal, 2-methyl- (9); (78-84-2)

Periodic acid (8,9); (10450-60-9)

(2SR,3SR)-2,4-DIMETHYL-3-HYDROXPENTANOIC ACID
(Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)-)



Submitted by Stephen H. Montgomery, Michael C. Pirrung, and
 Clayton H. Heathcock.¹

Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. *2,6-Dimethylphenyl propanoate.* To a 2-L, three-necked, round-bottomed flask is added 26.4 g (0.55 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 1). The sodium hydride is washed several times by decantation with dry hexane and is then covered with 1 L of dry ether (Note 2). The flask is immersed in an ice bath and equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser. A solution of 61.1 g (0.50 mol) of 2,6-dimethylphenol (Note 3) in 150 mL of dry ether is added dropwise over a

10-min period and the mixture is stirred for 5 min, during which time hydrogen evolution ceases. The cold solution is stirred continuously while a solution of 48 mL (60.9 g, 0.55 mol) of propanoyl chloride (Note 1) in 100 mL of dry ether is added dropwise over a 30-min period. After stirring for a further 1-hr the reaction mixture is poured into a 2-L separatory funnel containing 200 mL of water. The mixture is shaken vigorously and the ether layer is separated and washed successively with 200 mL of aqueous 10% sodium hydroxide, 200 mL of water, and 200 mL of 4% hydrochloric acid, then dried over magnesium sulfate. The ether is removed with a rotary evaporator and the residue distilled through a short, indented Claisen apparatus to obtain 85-86 g (96-97%) of 2,6-dimethylphenyl propanoate, bp 60-65°C (0.05 mm) (Note 4).

B. *2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate*. The reaction is carried out in a 2-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, and a 500-mL, pressure-equalizing dropping funnel. The dropping funnel is marked to hold 325 mL and is topped with a rubber septum pierced with a syringe needle attached to a source of dry nitrogen. The flask is charged with 300 mL of dry tetrahydrofuran (Note 2) and 69 mL (0.49 mol) of diisopropylamine (Note 1). Butyllithium (325 mL, 0.49 mol, 1.5 M in hexane) (Note 5) is transferred into the addition funnel with a cannula. The reaction flask and its contents are cooled to below -5°C by immersion in a bath of dry ice and isopropyl alcohol which is maintained at -10 to -15°C by periodic additions of dry ice. The butyllithium is added dropwise at such a rate as to maintain the temperature of the reaction mixture in the range 0 to -5°C. After the addition is complete the mixture is stirred for an additional 15 min and is then cooled to -70°C. While the reaction mixture is cooling, the septum is briefly removed and a solution of 85 g (0.48 mol) of 2,6-dimethylphenyl propanoate in 100 mL

of dry tetrahydrofuran is added to the addition funnel, the septum is replaced, and nitrogen is passed through the apparatus in a slow stream for 5 min. The ester is then added to the lithium diisopropylamide solution at such a rate that the temperature of the reaction mixture does not exceed -65°C . The total addition time is 30-40 min. After the addition is complete the reaction mixture is kept at -70°C for an additional hour during which time the dropping funnel is charged with a solution of 35.3 g (0.49 mol) of 2-methylpropanal (Note 1) in 100 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirred enolate solution at such a rate as to maintain a reaction temperature of less than -65°C . After the addition is complete the reaction mixture is kept at -70°C for an additional 30 min. To the vigorously stirred solution is added 500 mL of saturated aqueous ammonium chloride. At this point stirring is discontinued, the cooling bath is removed, and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a large separatory funnel and diluted with 500 mL of ether. The layers are separated and the organic phase is washed with 300 mL of water and 300 mL of saturated brine and then dried over magnesium sulfate. After removal of the drying agent the solvents are removed with a rotary evaporator to give 112-120 g of an oily semisolid, which is a 7:2 mixture of the β -hydroxy ester and 2,6-dimethylphenyl propanoate. This material may be crystallized from ether-hexane to provide 70 g (60%) of pure β -hydroxy ester, mp $75.5\text{--}76^{\circ}\text{C}$ (Note 6). However, it is not necessary to purify the crude product before hydrolysis to the β -hydroxy acid (Note 7).

C. (2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic acid. The crude product from the foregoing preparation (112-120 g) is dissolved in 500 mL of methanol and placed in a 2-L Erlenmeyer flask. A solution of 112 g (2 mol) of potassium hydroxide in a mixture of 500 mL of water and 500 mL of methanol is added with stirring, whereupon the reaction mixture warms to about 40°C. After stirring for 15 min crushed dry ice is added in portions to the vigorously stirred mixture until the pH is 7-8. The resulting solution is concentrated to a volume of about 500 mL with a rotary evaporator and extracted with two 300-mL portions of methylene chloride, which are discarded. The aqueous phase is then acidified to pH 1-2 by addition of 75 mL of concentrated hydrochloric acid (vigorous evolution of CO₂) and extracted with two 500-mL portions of methylene chloride. The combined organic extracts are washed with 200 mL of saturated brine and dried over magnesium sulfate. After removal of the drying agent the solvent is removed with a rotary evaporator to obtain 36-53 g of (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoic acid as a semisolid. Crystallization from hexane provides 30-43 g (41-60% overall yield) of pure hydroxy acid, mp 76-79°C (Note 8).

2. Notes

1. Sodium hydride was obtained from Ventron Corporation, Beverly, Massachusetts. 2,6-Dimethylphenol and propanoyl chloride were obtained from Aldrich Chemical Company and used without further purification. Diisopropylamine was distilled from calcium hydride prior to use. 2-Methylpropanal was distilled prior to use.

2. Reagent grade diethyl ether from a freshly opened container was used without further purification. Reagent grade tetrahydrofuran was dried over sodium before use.

3. 2,6-Dimethylphenol is a corrosive, poisonous substance which is readily absorbed through the skin. All reactions should be carried out in an efficient hood and appropriate protective apparel should be used.

4. The infrared spectrum (neat) shows an absorption at 1755 cm^{-1} . The ^1H NMR spectrum (CDCl_3) is as follows δ : 1.27 (t, 3 H, $J = 7$), 2.13 (s, 6 H), 2.55 (q, 2 H, $J = 7$), 6.90 (s, 3 H).

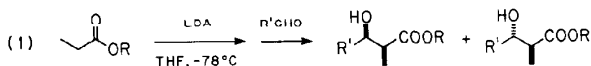
5. Butyllithium was obtained from Foote Mineral Company, Johnsonville, Tennessee. It may be standardized by a double titration procedure.²

6. The infrared spectrum (neat) has absorptions at 3500 and 1750 cm^{-1} . The ^1H NMR spectrum is as follows δ : 1.00 (d, 3 H, $J = 7$), 1.07 (d, 3 H, $J = 7$), 1.40 (d, 3 H, $J = 7$), 2.20 (s, 6 H), 2.93 (quintet 1 H, $J = 7$), 3.50 (m, 2 H), 7.03 (s, 3 H).

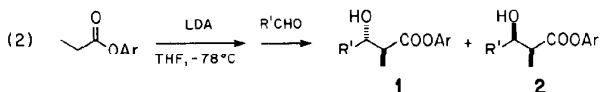
7. The checkers found that hydrolysis of once-crystallized aldol (mp $74-75^\circ\text{C}$) gives a hydroxy acid that crystallizes readily from hexane, for an overall-two step yield of 32%. Hydrolysis of the crude aldol product gives the hydroxy acid as an oil that crystallizes with difficulty, for an overall two-step yield of 45%.

8. The infrared spectrum (neat) has absorptions at 3500, 3300-2500, and 1695 cm^{-1} . The ^1H NMR spectrum is as follows δ : 0.93 (d, 3 H $J = 7$) 0.99 (d, 3 H, $J = 7$), 1.24 (d, 3 H, $J = 7$), 1.81 (octet, 1 H, $J = 6$), 2.69 (quintet, 1 H, $J = 7$), 3.44 (t, 1 H, $J = 5.6$), 7.4 (br s, 2 H, OH).

A number of methods have been developed for accomplishing aldol addition reactions in a stereoselective manner.³ The preformed lithium enolates of alkyl esters normally react with aldehydes to give mixtures of the two diastereomeric β -hydroxy esters (eq 1).⁴ However, the enolates derived from

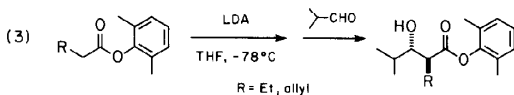


certain aryl esters add to aldehydes to give largely one stereoisomeric product (eq 2).⁵ The aryl groups that have been investigated are 2,6-



dimethylphenyl (DMP), 2,6-di-*tert* butyl 4-methylphenyl (BHT), and 2,6-di-*tert*-butyl-4-methoxyphenyl (DBHA). Selected examples are shown in Table I. The most convenient reagents, because of the ease of their further manipulations, are the DMP esters. With aliphatic aldehydes branched at the α -carbon, the DMP esters give essentially one diastereomeric product, β -hydroxy ester 1. With aromatic and α -unbranched aliphatic aldehydes, the DMP esters give predominantly, but not entirely, one isomer. In these cases the BHT or DBHA esters may be used. Acrolein gives a mixture of 1 and 2 even with the BHT and DBHA esters.

Aryl esters of other acids show similar stereoselectivity; examples are shown in eq 3. In addition, the BHT esters of O-benzylsuccinic acid condense



with aldehydes to give diastereomerically homogeneous adducts (eq 4).⁶

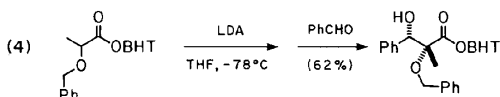


TABLE I
CONDENSATION OF ARYL ESTERS WITH ALDEHYDES

Ar	R Yield, % ^a	1:2	mp, °C	
DMP	C ₆ H ₅ -	72	88/12	62-63 ^c
DMP	n-C ₆ H ₁₁	70	86/14	oil
DMP	i-C ₃ H ₇ -	78	>98/2	76
DMP	t-C ₄ H ₉ -	82	>98/2	70-71
DMP	C ₆ H ₅ (CH ₃)CH-	81	>98/2	oil ^d
BHT	CH ₂ =CH-	88	85/15	64-67 ^e
BIT	CH ₂ -C(CH ₃)-	88	>98/2	70-71
BHT	C ₆ H ₅ -	96	>98/2	oil
BHT	i-C ₃ H ₇ -	100 ^b	>98/2	105-106
BHT	C ₆ H ₅ (CH ₃)CH-	100 ^b	>98/2	oil ^d
DBHA	CH ₂ =CH-	90	87/13	65-72 ^f
DBHA	C ₆ H ₅ -	75	>98/2	59-61
DBHA	n-C ₅ H ₁₁ -	70	>98/2	oil
DBHA	i-C ₃ H ₇ -	79	>98/2	91-93
DBHA	t-C ₄ H ₉ -	77	>98/2	88-89

a. All reactions were carried out on a 1-mmol scale. Unless otherwise noted, yields are for hplc-purified product. On a larger scale, such as is given in this procedure, yields are somewhat lower.

b. This is the yield of crude product; these products were not purified by chromatography.

c. Melting point given is that of the major diastereomer (1).

- d. Mixture of Cram's rule and anti-Cram's rule diastereomers: ratio = 4:1.
 - e. Melting point given is for a 95:5 mixture of 1:2.
 - f. Melting point given is for a 90:10 mixture of 1:2.
-
1. Department of Chemistry, University of California, Berkeley, CA 94720.
 2. Jones, R. G.; Gilman, H. In "Organic Reactions", Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, p 353.
 3. (a) Heathcock, C. H. In "Comprehensive Carbanion Chemistry", Durst, T.; Buncl, E., Eds.; Elsevier: New York, 1984; Vol. II; (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In "Topics in Stereochemistry", Eliel, E. L.; Allinger, N. L.; Wilen, S. H., Eds.; Wiley: 1982; Vol. 13; (c) Heathcock, C. H. In "Asymmetric Synthesis", Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3.
 4. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45* 1066.
 5. (a) Heathcock, C. H.; Pirrung, M. C. *J. Org. Chem.* **1980**, *45*, 1727; (b) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087.
 6. Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 4972.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic acid: Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)- (10); (73198-99-9)

2,6-Dimethylphenyl propanoate: Phenol, 2,6-dimethyl-, propanoate (9); (51233-80-8)

Sodium hydride (8,9); (7646-69-7)

2,6-Dimethylphenol: Phenol, 2,6-dimethyl- (9); (576-26-1)

Propanoyl chloride: Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

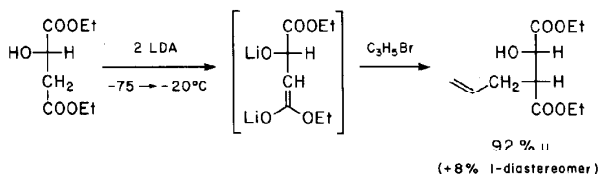
2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate: Pentanoic acid, 3-hydroxy-2,4-dimethyl-, 2,6-dimethylphenyl ester, (R*,R*)- (10); (73198-92-2)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

2-Methylpropanal: Isobutyraldehyde (8); Propanal, 2-methyl- (9); (78-84-2)

**DIASTEREOSELECTIVE α -ALKYLATION OF β -HYDROXYCARBOXYLIC ESTERS
THROUGH ALKOXIDE ENOLATES: (+)-DIETHYL (2S,3R)-3-ALLYL-2-HYDROXYSUCCINATE
FROM (-)-DIETHYL S-MALATE
(Butanedioic acid, 2-hydroxy-3-(2-propenyl)-,
diethyl ester, [S-(R,S)])**



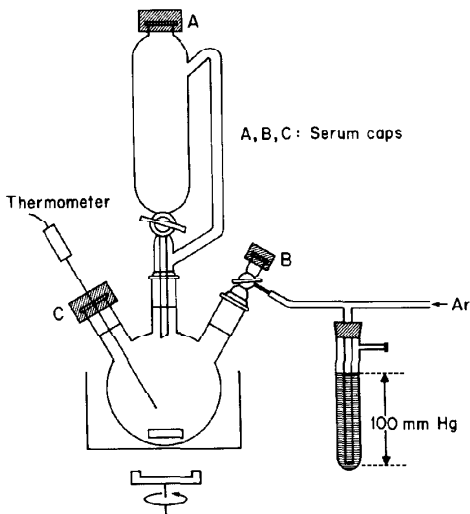
Submitted by Dieter Seebach, Johannes Aebi, and Daniel Wasmuth.¹

Checked by Brian Maxwell and Clayton H. Heathcock.

1. Procedure

A 500-mL, three-necked flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing and serum-capped dropping funnel, a three-way stop cock, and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm against the atmosphere until the aqueous workup (Note 2); see the accompanying figure.

The flask is charged through serum cap B with 17 mL (120 mmol) of diisopropylamine (Note 3) and 200 mL of tetrahydrofuran (THF) (Note 4), using syringe techniques. It is cooled to -75°C in a dry-ice bath. With stirring, exactly 100 mmol of butyllithium (hexane solution) (Note 5) is introduced from the dropping funnel (Note 6) within 10 min, followed after 0.5 hr, by a



mixture of 9.51 g (50 mmol) of (-)-diethyl (S)-malate (Note 7) and 5 mL of THF, which is added dropwise through cap B at such a rate that the temperature does not rise above -60°C . The addition takes approximately 10 min (Note 8). The dry-ice cooling bath is replaced by an ice salt bath (ca. 15°C) in which the contents of the flask warm to -20°C within 0.5 hr. The solution is stirred at $-20^{\circ} \pm 2^{\circ}\text{C}$ for 0.5 hr and then is cooled to -75°C .

To the solution of the alkoxide enolate thus prepared is added by syringe within 5 min 10.7 mL (124 mmol) of neat 3-bromo-1-propene (Note 9) at such a rate that the temperature of the reaction mixture does not rise above -70°C . Stirring is continued, first for 2 hr at -75°C , then overnight while the temperature rises to -5°C (Note 10).

The reaction mixture is quenched by adding a solution of 12 g (200 mmol) of glacial acetic acid in 20 mL of diethyl ether at -50°C and is then poured into a 1-L separatory funnel containing 500 mL of ether and 70 mL of water. The organic layer is washed successively with 40 mL each of saturated sodium bicarbonate and sodium chloride solution, and the aqueous phases are extracted with two 200-mL portions of ether. The combined ethereal solutions are dried by vigorous stirring with dry MgSO_4 for 15 min. Removal of the solvent first with a rotatory evaporator at a bath temperature no higher than 35°C and then at room temperature under oil pump vacuum (0.1 mm) furnishes 10.4 g of a yellow oil consisting, according to capillary GC (Note 11), of 81.3% of the desired allylated (2S,3R) product (73.5% yield), 8.5% of the (2S,3S) diastereomer (90.5% ds²), and 6.3% of the starting diethyl malate (Note 12).

The product is purified by flash chromatography (Notes 13-15): A flash column of 7-cm diameter is charged with 450 g of silica gel (Kieselgel 60, Merck, Korngrösse 0.040-0.063 mm, 230-400 mesh ASTM) and 10.4 g of the crude product. A 1:1 mixture of ether and pentane is used for elution, with a running rate of 5 cm column-length per min (pressure 1.25 atm). After a 200-mL forerun, 33-mL fractions are collected. No attempt is made to separate the two diastereomers; fractions 22-40 are combined to give 8.0 g (70%) of pure allylated product [ratio of diastereomers 92:8 (Note 11)], after removal of the solvent; $[\alpha]_{\text{D}}^{20} + 11.2^{\circ}$ (chloroform, c 2.23) (Note 16).

2. Notes

1. A Pt-100 thermometer (Testoterm KG, Lenzkirch, Germany) was used by the submitters. This is preferred to a conventional thermometer, because it is more accurate and more convenient to read. Careful temperature control is essential for the present procedure. Unless stated otherwise, all temperatures given are those of the reaction mixture. The checkers found that a +30 to -100°C alcohol thermometer is satisfactory.

2. The glass components of the apparatus are dried overnight in a 170°C oven and allowed to cool in a desiccator over a drying agent before assembly. The apparatus is filled with argon by evacuating and pressurizing several times through the three-way stop cock, as previously described.³

3. Diisopropylamine was freshly distilled from calcium hydride.

4. Tetrahydrofuran (THF) was first distilled under an inert atmosphere from KOH and then from the blue solution obtained with potassium and benzophenone, as described previously.³ [However, see warning notice, *Org. Synth., Collect. Vol. 5* 1973, 976-977.]

5. Before use, the commercial 1.6 M solution of butyllithium in hexane was titrated acidimetrically using diphenylacetic acid as an indicator.⁴

6. The dropping funnel was calibrated before use in this procedure. With standard graduated dropping funnels and syringes, the submitters noticed up to 10% deviation from true volumes! Syringe techniques were applied; the dropping funnel was rinsed with ca. 5 mL of dry THF.

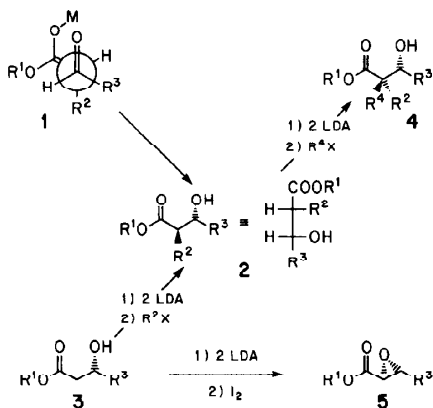
7. Commercial (S)-(-)-malic acid was esterified under standard conditions, following a procedure by Fischer and Speier.⁵ The freshly distilled ester employed by the submitters had an $[\alpha]_D^{20} = 10.5^\circ$ (neat) ($d_{20}^{40} = 1.128 \text{ g/cm}^3$), which corresponds to an optical purity of 100%.⁶

8. The flask, in which the ester/THF mixture was prepared, and the syringe are rinsed with a total of ca. 5 mL of dry THF.
9. Commercial allyl bromide was distilled before use.
10. The submitters used a 2-L Dewar cylinder holding, besides the flask, ca. 1 L of ethanol as a cooling liquid. If no excess dry ice was present at the beginning of the warm-up period, it took ca. 12 hr to reach -5°C .
11. GLC-analysis were performed using the following column and conditions: 0.3 mm x 20 m glass capillary column Pluronic L 64, program 120°C , (3 min), $10^{\circ}\text{C}/\text{min}$ up to 200°C , temperature of injector and detector 200°C , carrier gas: hydrogen (1.3 atm).
12. A total of ca. 4% of four minor side products with longer retention times is also present.
13. This is the fastest method, although it consumes large amounts of solvent and of silica gel. The procedure is that of Still, et al.⁷ Conventional chromatography is also possible, but is more time consuming.
14. Kugelrohr distillation does not separate the starting material, diethyl malate. Distillation through a 30-cm Vigreux column (silvered vacuum jacket) leads to loss of material (only 40% yield, diastereomer ratio 90:10, free of starting material).
15. Hydrolysis of the crude product yields pure (2S,3R)-3-allyl-2-hydroxysuccinic acid, mp $96.0\text{--}97.5^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20} + 14.7^{\circ}$ (acetone, c 1.69).
16. The boiling point is $77\text{--}78^{\circ}\text{C}$ (0.07 mm). Previously, a specific rotation of $[\alpha]_{\text{D}}^{25} + 11.9^{\circ}$ (chloroform, c 1.77) was reported.^{8a} The ^{13}C NMR spectrum (CDCl_3) of the (2S,3R) isomer shows the following signals δ (off-resonance multiplicity, assignment): 14.12 (q, $\text{CO}_2\text{CH}_2\text{CH}_3$), 32.21 (t, $\text{C}(3)\text{CH}_2$), 40.25 (d, $\text{C}(3)$), 60.06 and 61.01 (2 t, $\text{CO}_2\text{CH}_2\text{CH}_3$), 70.36 (d, $\text{C}(2)$), 117.78 (t, $\text{C}(3)\text{CH}_2\text{CH}=\text{CH}_2$), 134.94 (d, $\text{C}(3)\text{CH}_2\text{CH}=\text{CH}_2$), 171.92 and 173.48 (2 s, $\text{CO}_2\text{CH}_2\text{CH}_3$).

3. Discussion

The compound described here had not been known prior to our first synthesis of it.⁸ Generally, aldol derivatives of this configuration are prepared by the addition of E enolates of esters to aldehydes,^{9,10} 1 → 2 in Scheme 1. The method of preparing α-branched β-hydroxy esters by

Scheme 1

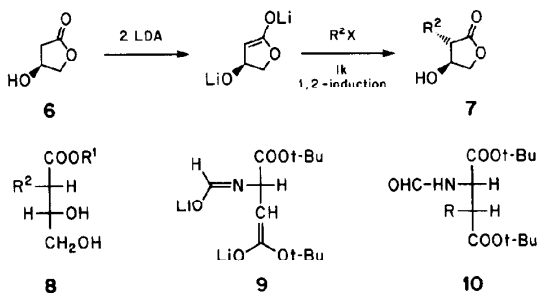


alkylation of dianion derivatives of the parent compounds was first discovered by Herrmann and Schlessinger.¹¹ It is highly diastereoselective¹² and

applicable without racemization to optically active derivatives, as first demonstrated independently by Fráter with β -hydroxybutanoate¹³ and by us with malate^{8,14} (see $3 \rightarrow 2$ and $3 \rightarrow 5$ in Scheme 1). In the meantime, many applications have been published.^{15,16} A related method of preparing derivatives belonging to the same diastereomeric series is the alkylation of β -lactone enolates.¹⁷

Examples of alkylation of malic esters are listed in Table I, together with those of double alkylation, which can also be achieved, see $2 \rightarrow 4$ in Scheme 1. Since the (S) and the (R) forms of malic acid are both readily available,¹⁸ the enantiomers of all structures shown in Table I can be

° Scheme 2



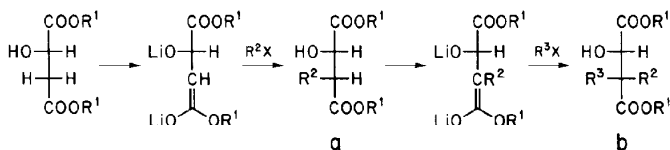
prepared as well. The method is also applicable to β -hydroxy γ -lactones of type 6, the alkylations of which lead¹⁹ to derivatives of opposite configuration 8, see $6 \rightarrow 7$ in Scheme 2. Finally, the dilithio derivative 9 of di-t-butyl N-formylaspartate is alkylated (\rightarrow 10, see Scheme 2)²⁰ with the same relative topology,²¹ as the malate dianion derivative (Table I).

In Table II, a series of useful chiral building blocks is shown, which are accessible through alkylations of malic acid derivatives; the table also contains some natural products which were synthesized from such building blocks.

The alkylation of doubly deprotonated β -hydroxy esters, an example of which is described in the procedure above, is not just a useful alternative to the diastereoselective aldol-type addition, but can supply enantiomerically pure products from appropriate precursors, and it can be used for the preparation of α,α -disubstituted derivatives (see 4 in Scheme 1). These were hitherto not available stereoselectively from enolates of α -branched esters and aldehydes.

TABLE I

PRODUCTS OF MONO- AND DIALKYLATION WITH RELATIVE TOPICITY u^a OF (S)-MALIC ESTERS THROUGH ALKOXIDE ENOLATES. THE RATIOS OF DIASTEREOMERS (SEE % ds) WAS DETERMINED BY ^1H or ^{13}C NMR SPECTROSCOPY OR BY GC ANALYSIS.



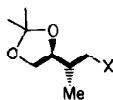
Product	R ¹	R ²	R ³	% Yield	% ds ^b	ref
(malate → a)						
a	CH ₃	CH ₃	-	65	91	8a, 14b
	CH ₃	C(OH)(CH ₃) ₂	-	55	75	8a
	C ₂ H ₅	CH ₃	-	88	91	8a
	C ₂ H ₅	CH ₂ C ₆ H ₅	-	48	91	8a
	C ₂ H ₅	I	-	80	67	8a
	CH ₃	CH ₂ CH ₂ NO ₂	-	31	85	14a
	CH ₃	C ₂ H ₅	-	64	90	14b
	CH ₃	CH ₂ CH=CH ₂	-	63	93	8b, 14c
(a + b)						
b	CH ₃	CH ₃	CH ₃	94	-	14b
	CH ₃	CH ₃	C ₂ H ₅	36	95	14b
	CH ₃	C ₂ H ₅	CH ₃		72	14b
	CH ₃	CH ₃	CD ₃	92	89	14b
	CH ₃	CH ₃	¹³ CH ₃	81	88	14b
	CH ₃	CH ₃	CH ₂ CH=CH ₂	74	95	14c
	CH ₃	CH ₃	H	100	67	14c

^aSee reference 21. ^bSee reference 2.

TABLE II

CHIRAL, NON-RACEMIC BUILDING BLOCKS AND NATURAL PRODUCTS SYNTHESIZED THROUGH ALKYLATION OF MALIC ACID DERIVATIVES. THE FOUR-CARBON UNIT OF THE STRUCTURE WHICH IS DERIVED FROM MALIC ACID IS INDICATED BY HEAVY LINES.

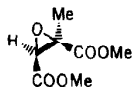
PRODUCTS AND INTERMEDIATES FROM (S)-MALIC ACID



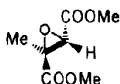
ref. 13b, 22



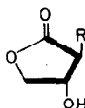
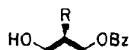
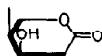
ref. 6b



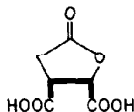
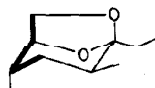
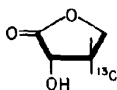
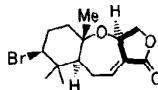
ref. 14c



ref. 14c

R = Me, Et, higher alkyl,
allyl, benzyl; ref. 19R = Me, allyl, benzyl
(by oxidative degradation
after alkylation); ref. 8c

ref. 23

(+)-isocitric acid
ref. 8b(-)-8-multistriatin
ref. 15b, 22(+)-pantolactone
ref. 14b(-)-aplysistatin
ref. 19c

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

(+)-Diethyl (2S,3R)-3-allyl-2-hydroxysuccinate: Butanedioic acid, 2-hydroxy-3-(2-propenyl)-, diethyl ester, [S-(R*,S*)]- (9); (73837-97-5)

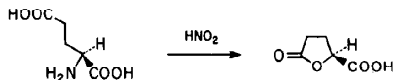
(-)-Diethyl S-malate: Malic acid, diethyl ester, (S)- (8); Butanedioic acid, hydroxy-, diethyl ester, (S)- (9); (691-84-9)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

3-Bromo-1-propene: 1-Propene, 3-bromo- (8,9); (106-95-6)

(S)-(+)- γ -BUTYROLACTONE- γ -CARBOXYLIC ACID
(2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)-)



Submitted by Olivier H. Gringore and Francis P. Rouessac.¹

Checked by Matthew F. Schlecht, Howard Drossman, and
 Clayton H. Heathcock.

1. Procedure

Caution! This procedure should be conducted in a well-ventilated hood to avoid inhalation of poisonous NO₂ vapor. To protect the operator the distillation must be carried out with the usual precautions associated with vacuum distillation.

A 6-L Erlenmeyer flask which contains a large magnetic stirring bar is charged with 294 g (2 mol) of L-glutamic acid (Note 1) and 2 L of distilled water. The suspension is stirred vigorously while solutions of 168 g (2.4 mol) of sodium nitrite in 1.2 L of water and 1.2 L of aqueous 2 N sulfuric acid are added simultaneously from separatory funnels (Note 2). After the addition is complete (Note 3), the solution is stirred at room temperature for an additional 15 hr. The water is then removed by heating below 50°C under reduced pressure with a rotary evaporator (Note 4). The resulting pasty solid is triturated with 500 mL of boiling acetone and the hot solution is filtered

and set aside to cool. This operation is repeated four times (Notes 5 and 6). Removal of solvent with a rotary evaporator affords 312 g of crude (+)- γ -butyrolactone- γ -carboxylic acid as a slightly yellow oil (Notes 7 and 8).

A 250-mL, round-bottomed flask is equipped with a magnetic stirring bar and charged with 100 g of the foregoing crude lactone acid (Note 9). The flask is fitted with a Claisen distillation apparatus and connected to a vacuum pump (Notes 10 and 11). The flask is gradually heated with an oil bath (160°C) until gas evolution ceases (Note 12). At this point the oil bath is removed and the black, viscous oil is distilled with the use of a flame (Note 13). The product, 58 g (70%), is collected as a colorless oil at 146-154°C (0.03 mm). The distillate crystallizes in the receiver, mp 66-68°C (Notes 14 and 15).

2. Notes

1. This material was purchased from the Aldrich Chemical Company Inc., $[\alpha]_D^{23} + 29^\circ$ (6 N HCl, c 1).

2. The addition requires about 30 min. During addition the reaction mixture should warm to 30-35°C and smooth evolution of NO_2 and N_2 should occur. If the solutions of NaNO_2 and H_2SO_4 are added too rapidly, more gas appears to be generated and a reduction in yield occurs.

3. At this point the reaction mixture is clear and colorless. Residual brown gas usually remains in the flask.

4. If a conventional aspirator pump is employed, concentration can require several days. The checkers employed a rotary evaporator that was evacuated to approximately 3 mm by a vacuum pump. Two traps, one cooled in an ice-salt bath and the other in an acetone/dry-ice bath, were inserted between

the rotary evaporator and the vacuum pump. In this way, the reaction mixture can be concentrated to a paste in about 16-20 hr.

5. Repetitive extraction may also be performed in a flask heated with a water bath to 65°C; acetone is removed by decantation. Ethyl acetate has also been used for the extraction.²

6. The checkers found that a higher recovery is obtained if the pasty solid is vigorously agitated during trituration with five 750-mL portions of boiling acetone.

7. The crude yield reported is in excess of the theoretical yield (260 g). The checkers obtained crude yields of 243-259 g, probably because water was more efficiently removed in the concentration step.

8. Although this material is sufficiently pure for some applications, it is advisable to purify it further before use. Distillation² and crystallization³ have been described. The submitters recommend purification by the distillation procedure given. By direct crystallization of 101 g of crude lactone acid from ether/petroleum ether, the checkers obtained 36.5 g (35%) of material, mp 72-74°C.

9. If the distillation is carried out on a larger scale, the yield is lower.

10. The submitters recommend a short path distillation apparatus with large sections (i.e., wide bore) since the distillate partially crystallizes in the condenser during the distillation. It is important that the distillation apparatus have a Claisen head because the viscous material tends to bump.

11. The vacuum pump should be protected by a soda-lime trap.

12. During this heating period the system pressure should rise from 0.03 mm to 0.5 mm and the crude lactone acid should become black. When gas evolution ceases, the pressure decreases to its initial value.

13. Distillation should be carried out briskly. If a simple bunsen burner with a low flame is used, distillation requires several hours. The checkers used a hot flame, about 13 cm in length, from a gas-air torch. In this way, the distillation requires only about 15 min. Distillation is discontinued when colored vapors appear.

14. The checkers distilled crude lactone acid obtained in approximately quantitative yield (259 g). When this material was used, distillation of 100-g portions gave 64.3-66.4 g (65-66% yield).

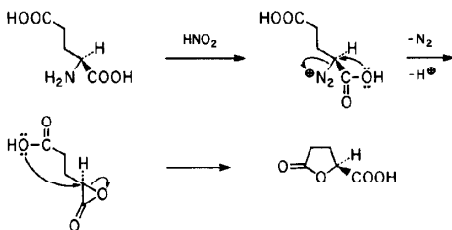
15. The submitters report that recrystallization from ethyl acetate-petroleum ether raises the melting point to 73°C. The product obtained is analytically pure, $[\alpha]_D^{21} + 16^\circ$ (EtOH, c 2). When the checkers used ethyl acetate-petroleum ether they often obtained an oily product.

The spectrum of the lactone acid is as follows: ^1H NMR (CD_3COCD_3) δ : 2.1-2.9 (m, 4 H), 4.85-5.15 (m, 1 H), 5.1 (s, 1 H, COOH).

3. Discussion

The (S)-(+)- γ -butyrolactone- γ -carboxylic acid is a useful intermediate for the synthesis of pheromones,⁴ natural lignans,⁵ and other derivatives.⁶ In the same manner, but starting with D-glutamic acid, the (R)-(-)-lactone acid may be prepared.⁷ Lactonization occurs with full retention of configuration at the chiral center.^{8,9} Recently, authors have described an efficient method which allows the formation of derivatives of the (R)-(-)-lactone from the more available (S)-(+)-counterpart.¹⁰

The procedure is a detailed description of the Austin and Howard preparation.² The mechanism presumably involves anchimeric assistance of the carboxy group in decomposition of an intermediate diazonium ion, leading to a labile α -lactone:⁴



The title compound has also been prepared¹¹ using hydrochloric acid instead of sulfuric acid, and ethyl acetate instead of acetone. In the hands of the submitters, this procedure gave a lower yield.

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Appendix

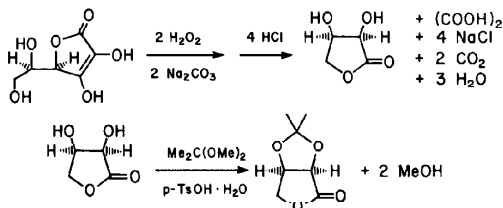
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(S)-(+)- γ -Butyrolactone- γ -carboxylic acid: 2-Furoic acid, tetrahydro-5-oxo-,
 (S)-(-)- (8); 2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)- (9);
 (21461-84-7)
 L-Glutamic acid (8,9); (56-86-0)

2,3-O-ISOPROPYLIDENE-D-ERYTHRONOLACTONE

(Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-(3aR-cis)-)



Submitted by Noal Cohen, Bruce L. Banner, Anthony J. Laurenzano,
and Louis Carozza.¹

Checked by Lee A. Flippin and Clayton H. Heathcock.

1. Procedure

A 1-L. three-necked, round-bottomed flask fitted with a thermometer, addition funnel, and an air motor-driven paddle stirrer is charged with 35.2 g (0.20 mol) of erythorbic acid (Note 1) and 500 mL of deionized water. The solution is stirred with ice bath cooling (Note 2) and 42.4 g (0.40 mol) of anhydrous, powdered sodium carbonate (Note 3) is added in small portions (Note 4). The resulting yellow solution (Note 5) is stirred with ice bath cooling while 44 mL (0.45 mmol) of 31.3% by weight aqueous hydrogen peroxide (Note 6) is added dropwise over a 10-min period. The internal temperature rises from 6°C to 19°C (Note 7). The solution, containing a few solid particles, is stirred for 5 min with ice bath cooling, during which time the internal

temperature continues to rise to 27°C. The flask is now immersed in a water bath which is heated to 42°C. The solution is stirred for 30 min, during which time the internal temperature reaches a maximum of 42°C (Note 8). Norit A (8 g) is added in portions over 10 min to decompose the excess peroxide and the mixture is heated on a steam bath with continued stirring for 30 min, at which point gas evolution has essentially ceased and a negative starch-iodide test is observed. The internal temperature reaches and is kept at 75-78°C. The hot mixture is filtered with suction on a Celite pad into a 2-L, three-necked, round-bottomed flask and the filter cake is washed, in several small portions, with a total of 100 mL of deionized water. The combined filtrate and washes are acidified to pH 1 by the *cautious* (Note 9) addition of 150 mL (0.90 mol) of 6 N aqueous hydrochloric acid, in portions, with swirling. The acidic solution is concentrated with a rotary evaporator at 50°C/water aspirator pressure. The residue is dried at 50°C/0.2 mm, to give 84.6 g of a pale-yellow solid residue containing D-erythronolactone, oxalic acid, and sodium chloride (Notes 10, 11). To this material is added 175 mL of acetone (Note 13) and the mixture is swirled to loosen the solids caked on the sides of the flask. A 50-g portion of anhydrous, powdered magnesium sulfate (Note 14) is now added and the mixture is stirred by means of an air motor-driven paddle stirrer as 350 mL (2.85 mol) of 2,2-dimethoxypropane (Note 15) is added in one portion. To the stirred mixture is added 0.42 g (0.0022 mol) of p-toluenesulfonic acid monohydrate, at room temperature. The slurry is blanketed with nitrogen and stirred at room temperature for 18 hr. In a 2-L, three-necked, round-bottomed flask fitted with a thermometer and an air motor-driven paddle stirrer, a mixture of 500 mL of anhydrous ether and 61.3 mL (0.44 mol) of triethylamine (Note 16) is cooled in an ice bath to 5°C. The reaction mixture is decanted into this solution. The residual solids are

rinsed with 60 mL of ether which is also decanted into the triethylamine solution. After being stirred for a few minutes (Note 17), the mixture is filtered with suction on a 600-mL, coarse, sintered glass funnel. The solids are washed thoroughly with a total of 300 mL of anhydrous ether by slurrying three times on the funnel with the vacuum turned off; the vacuum is then applied to draw the wash ether through the funnel. The filtrate and washes are combined and concentrated with a rotary evaporator at water aspirator pressure, and the residue is dried at 45°C/0.5 mm, to give 34.3 g of a pale-yellow solid (Note 18). This material is dissolved in approximately 150 mL of 1:1 hexanes-ethyl acetate and the solution (Note 19) is adsorbed on a column of 200 g of silica gel (Note 20) packed in 1:1 hexanes-ethyl acetate. The column is eluted with a total volume of 2 L of 1:1 hexanes-ethyl acetate (Note 21). The eluate is concentrated with a rotary evaporator at aspirator pressure and the solid residue is dried under high vacuum to afford 27.3 g of a colorless solid. This material, contained in a 1-L. one-necked, round-bottomed flask, is treated with 150 mL of anhydrous ether and the mixture is refluxed on a steam bath for 5 min to dissolve all the solid. The solution is removed from the steam bath and treated with 225 mL of hexanes. An immediate precipitate results. The mixture is refrigerated (0°C) for 3.5 hr and then filtered with suction. The solid is washed with a total of 100 mL of hexanes, in small portions, and then dried under high vacuum at 20°C. There is obtained 23.6 g (74.7%) of 2,3-O-isopropylidene-D-erythrionolactone as a white solid, mp 65.5-66°C, $[\alpha]_D^{25}$ -113.8° (c 1.11 H₂O) (Notes 22, 23, 24, 25).

2. Notes

1. Erythorbic acid is the same compound as D-isoascorbic acid, available from the Aldrich Chemical Company, Inc. This substance is also known as araboascorbic acid.

2. The internal temperature is 6°C initially.

3. Sodium carbonate was obtained from the Fisher Scientific Company.

4. Vigorous evolution of carbon dioxide is observed. The internal temperature rises to 8°C.

5. A few particles of undissolved sodium carbonate may remain.

6. Aqueous hydrogen peroxide was obtained from the Fisher Scientific Company. The lot analysis given on the bottle is used to calculate the volume of hydrogen peroxide solution required. Approximately 10% molar excess of peroxide appears to be required to provide a clean product.

7. The oxidation is quite exothermic. Attempts to increase the concentrations of the reactants led to an exotherm which was difficult to control and which was complicated by the precipitation of solids which hampered stirring.

8. A small amount of gas evolution is noted during this period.

9. Evolution of carbon dioxide is vigorous.

10. It is essential that all the water be removed at this point and that a constant weight of approximately 84 g be obtained.

11. If desired, D-erythronolactone can be isolated at this point by treatment of the residue with boiling ethyl acetate. On this scale, the solid is triturated at reflux with 325 mL of ethyl acetate for 5 min. The solution is decanted and the trituration is repeated with 130 mL of ethyl acetate. The combined solutions are cooled to 5°C and filtered. The solid is washed with

portions with a total of 400 mL of cold ethyl acetate. After air drying, there is obtained 15.4 g (77.0%) of D-erythronolactone as a white solid, mp 97.5-99.5°C, $[\alpha]_D^{25} - 72.8^\circ$ (H₂O, *c* 0.498) (Note 12).

12. The physical properties of D-erythronolactone are as follows: Lit.² mp 104-105°C, $[\alpha]_D^{20} - 73.2^\circ$ (H₂O, *c* 0.533).

13. Acetone was obtained from Fisher Scientific Company.

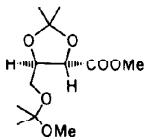
14. The drying agent is added to remove any residual moisture and to facilitate the subsequent filtration.

15. 2,2-Dimethoxypropane was obtained from the Aldrich Chemical Company, Inc.

16. Triethylamine was obtained from Eastman Chemical Products, Inc.

17. The mixture is alkaline to pH paper.

18. TLC analysis of the crude product (1:3 hexane-ethyl acetate, EM Silica Gel 60 F-254 plates) reveals the desired acetonide lactone to be the major component (*R_f* 0.6) with one minor, less polar impurity and several minor, more polar impurities. The ¹H NMR and IR spectra of a pure sample of the less polar impurity (an oil) were compatible with the following structure:



¹H NMR (100 MHz, CDCl₃) δ : 1.31 (2 s, 6 H, (CH₃)₂C), 1.39 (s, 3 H, C₂-CH₃), 1.59 (s, 3 H, C₂-CH₃), 3.20 (s, 3 H, OCH₃), 3.41 (dd, 1 H, *J* = 6, 10.5, CH₂O), 3.57 (dd, 1 H, *J* = 4.5, 10.5, CH₂O), 3.76 (s, 3 H, CO₂CH₃), 4.49 (m, 1 H, H₅), 4.67 (d, 1 H, *J*_{4,5} = 7, H₄); IR (CHCl₃) cm⁻¹: 1760, 1735 (ester C=O).

19. A small amount of insoluble material is present.

20. EM Silica Gel 60, 0.063-0.2 mm was used. The column dimensions are approximately 1.75 in x 14 in.

21. TLC is utilized to insure that all of the desired product is eluted from the column. This procedure removes the minor, polar impurities present in the crude product which appear at or near the origin of the TLC plate.

22. This material is homogeneous on TLC analysis; ^1H NMR (100 MHz, CDCl_3) δ : 1.37 (s, 3 H, $\text{C}_2\text{-CH}_3$), 1.46 (s, 3 H, $\text{C}_2\text{-CH}_3$), 4.42 (d, 2 H, $J_{6,6a} = 2$, H_6), 4.75 (d, 1 H, $J_{3a,6a} = 6$, H_{3a}), 4.89 (dt, 1 H, $J_{3a,6a} = 6$, $J_{6,6a} = 2$, H_{6a}); IR (CHCl_3) cm^{-1} : 1786 (γ -lactone C=O).

23. The physical properties are as follows: Lit.³ mp 68-68.5°C, $[\alpha]_D^{20} -112^\circ$ (H_2O , c 1.5).

24. The reaction sequence has been run on a 176-g (1.0 mol) scale with no loss in yield.

25. The checkers obtained 22.5 g (71.1%) of product as a white solid, mp 68.0-68.5°C, $[\alpha]_D^{25} -123.4^\circ$ (H_2O , c 0.96). It is important that crystallization from the ether-hexane mixture be carried out at 0°C. In one run in which crystallization was carried out at 8°C, the checkers obtained only 15.3 g (48.4%) of product, mp 65.5-66.0°C.

3. Discussion

2,3-0-Isopropylidene-D-erythroneolactone and the corresponding lactol, 2,3-0-isopropylidene-D-erythrose are useful chiral synthons in the total synthesis of certain natural products such as the leukotrienes.⁴ The lactol is readily available from the lactone, in excellent yield, by reduction with diisobutylaluminum hydride.^{4,5} 2,3-0-Isopropylidene-L-erythrose has been employed as the starting material in an enantioselective synthesis of (+)-15S-

prostaglandin A₂.⁶ Optically pure, selectively protected, polyfunctional C₄-units such as these have great potential in synthesis if readily available, in substantial quantity, from inexpensive members of the "chiral pool".⁷

D-Erythrionolactone and/or its isopropylidene derivative have been prepared starting from L-rhamnose,⁸ D-ribose,⁹ D-ribonolactone,³ potassium D-glucuronate,¹⁰ D-glucose,¹¹ erythorbic acid,² by optical resolution of racemic erythrionolactone,¹² and by asymmetric total synthesis.¹³ 2,3-O-Isopropylidene-D-erythrose has been obtained from D-arabinose by a route which does not involve the intermediacy of the lactone.¹⁴ All of these processes suffer from either relatively low overall yields or the requirement of a large number of individual stages. The procedure described here, which is based on a similar oxidative degradation of L-ascorbic acid (vitamin C) to L-threonic acid,¹⁵ is undoubtedly the most expeditious route to the acetonide of D-erythrionolactone available. In addition, the starting material, erythorbic acid, is an inexpensive and readily available substance, commonly used as a food preservative. It is pertinent to note that recently L-ascorbic acid has itself found synthetic utility as a precursor to (R)-glycerol acetonide, an important C₃ chiral synthon.¹⁶

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,3-O-Isopropylidene-D-erythronolactone: Erythronic acid, 2,3-O-isopropylidene- γ -lactone, D- (8); Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-, (3aR-cis)- (9); (25581-41-3)

Erythorbic acid: D-*erythro*-Hex-2-enoic acid, γ -lactone (8,9); (89-65-6)

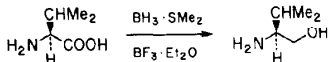
2,2-Dimethoxypropane: Acetone, dimethyl acetal (8); Propane, 2,2-dimethoxy- (9); (77-76-9)

p-Toluenesulfonic acid monohydrate: p-Toluenesulfonic acid (8);

Benzenesulfonic acid, 4-methyl- (9); (104-15-4)

L-VALINOL

(1-Butanol, 2-amino-3-methyl-, (S)-)



Submitted by G. A. Smith and Robert E. Gawley.¹

Checked by Karl M. Smith and Clayton H. Heathcock.

1. Procedure

Caution! Because of the foul odor of the methyl sulfide given off, this procedure, up to the methanol quench, should be carried out in a hood.

A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, heating mantle, 250-mL graduated addition funnel, and an 8 in. air-cooled reflux condenser (West type) topped with a water-cooled distillation head and a 1-L receiving flask. It is connected to a nitrogen line through the still head. The glassware is either oven dried and cooled in a desiccator or flame dried and assembled while still hot. The assembly is flushed with nitrogen, and charged with 200 g of L-valine (1.7 mol), 400 mL of tetrahydrofuran (THF) (Note 1), and 210 mL of freshly distilled boron trifluoride etherate (242 g, 1.7 mol). The mixture is heated at a rate sufficient to cause the THF to reflux gently (Note 2) and 188 mL (1.88 mol) of borane-methyl sulfide complex, BMS, (Note 3) is added dropwise over the course of 2 hr (Note 4). The solution is then refluxed for 18 hr. The methyl sulfide which has

collected at the stillhead is discarded (Note 5), and the reaction mixture is cooled to 0°C and quenched by the slow addition of 200 mL of methanol. The addition funnel is replaced by a glass stopper, and the air-cooled condenser is removed, leaving the flask equipped for distillation of solvent through the distillation head. The reaction mixture is concentrated under reduced pressure with heating and stirring. The distillation head is replaced by a water-cooled reflux condenser, and the residue is dissolved in 1 L of 6 M sodium hydroxide and refluxed for 4 hr. The mixture is saturated with potassium carbonate (ca. 400 g), cooled, filtered through a Celite pad on a coarse, fritted funnel, and extracted with three 1-L portions of chloroform. The combined extracts are washed with three portions of saturated sodium chloride (500 mL each), stirred over anhydrous potassium carbonate for 24 hr, and concentrated under reduced pressure to give a yellow oil. The crude material is vacuum distilled to give 77.5 g (44%) of purified L-valinol; bp 62-67°C/2.5 mm; $[\alpha]_D^{20} +14.6^\circ$ (neat), n_D^{20} 1.455; IR (neat film) cm^{-1} : 3300 (OH), and 1590 (NH_2); NMR δ : 0.92 (d, 6 H), 1.54 (m, 1 H), 2.38-2.74 (m, 4 H), 3.13-3.78 (m, 2 H).

2. Notes

1. Tetrahydrofuran is dried by distillation from sodium/benzophenone ketyl.
2. The temperature is maintained at a sufficiently high point so that THF refluxes in the air-cooled condenser while ether and methyl sulfide distill through the short path distillation head.
3. The borane-methyl sulfide complex is available from Aldrich Chemical Company, Inc.

4. It is important that gentle reflux be maintained throughout the addition. If the solution is not heated during this period, an exothermic reaction occurs when the solution is refluxed.

5. Methyl sulfide should be destroyed by slowly pouring the volatile distillate into 1 gallon of household bleach (5% sodium hypochlorite). After 30 min, the bleach solution may be discarded in the drain.

3. Discussion

Reduction of amino acids to the corresponding amino alcohols via their ethyl ester hydrochlorides has been reported using lithium aluminum hydride² and sodium borohydride.³ The ability to reduce amino acids with borane - methyl sulfide (BMS) and boron trifluoride etherate was reported in a patent.⁴ The present procedure is a hybrid of two procedures: Lane's procedure for the BMS/trimethyl borate reduction of anthranilic acid,⁵ and Brown's procedure for enhanced-rate reductions of several functional groups with BMS by distilling off the methyl sulfide during the course of the reaction.⁶ The submitters have obtained a 97% crude yield (44-51% yield after distillation) of prolinol using this procedure. Lane reports that the following additional amino acids may be reduced using BMS/BF₃ etherate: leucine, phenylalanine, and 6-aminocaproic acid.⁴ Meyers has added phenylglycine to the list, and has confirmed the optical purity of the amino alcohols obtained by preparation of the Mosher amides.⁷

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

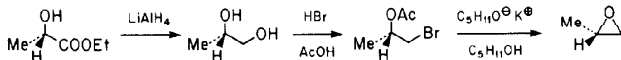
L-Valinol: 1-Butanol, 2-amino-3-methyl-, L- (8); 1-Butanol,
2-amino-3-methyl-, (S)- (9); (2026-40-4)

L-Valine (8,9); (72-18-4)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃)
(1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9):
(109-63-7)

Borane-methyl sulfide complex: Methyl sulfide, compd. with borane (1:1) (8);
Borane, compd. with thiobis[methane] (1:1) (9): (13292-87-0)

**OPTICALLY ACTIVE EPOXIDES FROM VICINAL DIOLS VIA
VICINAL ACETOXY BROMIDES: THE ENANTIOMERIC METHYLOXIRANES**



Submitted by Martin K. Ellis and Bernard T. Golding.¹

Checked by Stephen H. Montgomery and Clayton H. Heathcock.

1. Procedure

A. *(S)*-(+)-Propane-1,2-diol. Into a three-necked, 500-mL, round-bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser are placed 10.8 g (0.284 mol) of lithium aluminum hydride and 200 mL of dry ethyl ether. To this slurry is added, from the dropping funnel, 33 g (0.28 mol) of ethyl L-(-)-lactate (Note 1) in 150 mL of dry ethyl ether at a rate which maintains a steady reflux. The heterogeneous mixture is stirred for 3 hr. Then 25 mL (1.39 mol) of water is carefully added and stirring is continued for a further 1.5 hr. The mixture is filtered and the white solid (LiOH) is washed well with ether and dichloromethane. The organic phases are combined, dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator to give a portion of the crude product (3 g). Aqueous 1 M sulfuric acid is added to the solid until the milky suspension is just acidic (pH 6-6.5). The suspension is subjected to continuous extraction with twice its volume of dichloromethane (about 500 mL) for 168 hr. The

dichloromethane layer is dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator. The crude products are combined and distilled at reduced pressure to obtain 14.4-15.6 g (68-73%) of (S)-(+)-propane-1,2-diol, bp 52-56°C (0.5 mm), as a colorless liquid (Note 2).

B. (S)-(-)-2-Acetoxy-1-bromopropane. A three-necked, 100-mL, round-bottomed flask fitted with a magnetic stirring bar, dropping funnel and reflux condenser is charged with 7.6 g (0.1 mol) of (S)-(+)-propane-1,2-diol. A solution of 45% w/v hydrogen bromide-acetic acid (71 g, 0.3 mol) (Note 3) is added from the dropping funnel with cooling over ca. 5 min. The homogeneous solution is stirred at room temperature for 45 min, after which it is added to 200 mL of water and the mixture neutralized immediately with solid sodium carbonate (Note 4). The neutral solution is extracted three times with 150 mL of ethyl ether, the organic phases are combined, dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator. Distillation of the crude product at reduced pressure affords 14.1-15.4 g (78-85%) of (S)-(-)-2-acetoxy-1-bromopropane, bp 54-57°C (7 mm), as a colorless liquid (Note 5).

C. (S)-(-)-Methyloxirane. To a three-necked, 100-mL, round-bottomed flask equipped with a magnetic stirring bar, pressure equalizing dropping funnel and 10-cm Vigreux column connected to an efficiently-cooled condenser and receiver are added 9.05 g (50 mmol) of the acetoxybromopropane and 20 mL of dry 1-pentanol. The solution is stirred at room temperature and 41.66 mL (50 mmol) of 1.2 M potassium pentoxide in 1-pentanol (Note 6) is added from the dropping funnel over ca. 20 min. A white precipitate of potassium bromide is observed. After addition is complete the flask is warmed in an oil bath at ca. 130-145°C to attain distillation (Note 7). The product, (S)-(-)-methyloxirane, 2.0-2.35 g (69-81%), is collected as a colorless liquid, bp 34-35°C (Note 8).

2. Notes

1. Ethyl L-(-)-lactate was purchased from Fluka AG, Buchs, Switzerland and was used directly. Checkers found that fresh ethyl lactate purchased from Fluka is only 9/-98% ee, by ^{19}F NMR spectroscopy on the Mosher ester.

2. An optical rotation of $[\alpha]_D^{16} +20.3^\circ$ (H_2O , c 7.5), [lit.² $[\alpha]_D^{20} +20.7^\circ$ (H_2O , c 7.5)] was observed for this product. It had the following spectral properties: IR (liquid film, polystyrene reference) cm^{-1} : 3350 (s), 2970 (m), 2930 (m), 2870 (m), 1455 (m) 1375 (m); ^1H NMR (CDCl_3) δ : 1.15 (d, 3 H, $-\text{CH}_3$), 3.40 (q, 1 H, $\text{H}_2\text{C}(\text{OH})-$) and 3.59 (q, 1 H, $\text{H}_2\text{C}(\text{OH})-$), 3.89 (m, 1 H, $-\text{CH}(\text{OH}) \text{CH}_3$), $-\text{OH}$ resonances variable.

3. 45% Hydrogen bromide-acetic acid was purchased from BDH Chemicals Ltd., Poole, England. The checkers used hydrobromic acid (30-32% in acetic acid, 4.1 M) from Fisher Scientific, 711 Forbes Ave., Pittsburgh, PA 15219.

4. Approximately 80 g of sodium carbonate is required. On addition of solid sodium carbonate a considerable amount of frothing occurs. To prevent the loss of product, the addition of the reaction mixture to the water and subsequent neutralization with solid sodium carbonate is performed in a 2-L beaker.

5. An optical rotation of $[\alpha]_D^{20} -13.7^\circ$ (CHCl_3 , c 5.8), [lit.² $[\alpha]_D^{23} -13.55$ (CHCl_3 , c 5.8)] was observed for (S)-(-)-2-acetoxy-1-bromopropane. (R)-(+)-2-Acetoxy-1-bromopropane, obtained from (R)-(-)-propane-1,2-diol^{3,4} gave an optical rotation of $[\alpha]_D^{18} +14.1^\circ$ (CHCl_3 , c 5.8). Both enantiomers of acetoxybromopropane had the following spectral properties: IR (liquid film, polystyrene ref) cm^{-1} : 2980 (w), 2937 (w), 1735 (s), 1450 (w), 1425 (w) and 1370 (s); ^1H NMR (CCl_4) δ : 1.34 (d, 3 H, CH_3), 2.10 (s, 3 H, $-\text{OCOCH}_3$), 3.38 (d, 2 H, $-\text{CH}_2\text{Br}$), and 4.97 (m, 1 H, $-\text{CH}(\text{OCOCH}_3)\text{CH}_3$) due to 2-acetoxy-1-

bromopropane (94% by integration) and 1.70 (3 H) and 4.16 (3 H) due to 1-acetoxy-2-bromopropane (6%).

6. Potassium pentoxide in 1-pentanol is prepared by dissolving freshly cut potassium in dry, freshly-distilled 1-pentanol under nitrogen. The molarity of this solution may be determined by titration against standard aqueous acid.

7. The oil bath is pre-heated to 120-130°C. It is then transferred to a pre-warmed heater with stirrer upon a lab jack below the reaction flask. The oil bath can then be moved into position with the aid of the lab jack.

8. An optical rotation of $[\alpha]_D^{20} -18.7^\circ$ (CCl_4 , c 5.83), [lit.² $[\alpha]_D^{22} -18.55^\circ$ (CCl_4 , c 5.84)] was observed for (S)-(-)-methyloxirane. (R)-(+)-Methyloxirane, obtained from (R)-(+)-acetoxybromopropane (Note 5), gave an optical rotation of $[\alpha]_D^{18} +19.13^\circ$ (CCl_4 , c 5.66), [lit.² $[\alpha]_D^{20} +18.7^\circ$ (CCl_4 , c 5.83)], bp 34-35°C and a range of yields within the limits of those obtained for (S)-(-)-methyloxirane. Both enantiomers of methyloxirane had the following spectral properties; ^1H NMR (CCl_4) δ : 1.27 (d, 3 H, $-\text{CH}_3$), 2.27 (q, 1 H, $-\text{CH}(\text{O})\text{CH}_2$), 2.59 (t, 1 H, $-\text{CH}(\text{O})\text{CH}_2$) and 2.83 (m, 1 H, $\text{H}_3\text{C}-\text{CH}(\text{O})\text{CH}_3$) ppm.

3. Discussion

This procedure illustrates the stereospecific conversion of 1,2-diols into vicinal acetoxy bromides by hydrogen bromide in acetic acid.² The acetoxy bromides which are formed are easily transformed into epoxides by base treatment. In the examples presented, the base is used in a high boiling solvent to facilitate isolation of epoxide by direct distillation from the reaction mixture (see also refs. 5-8). For other examples, a solvent may be used which is either more volatile than the epoxide (e.g. methanol²) or easily

removed by aqueous work-up and solvent extraction of the epoxide (e.g. ethane-1,2-diol⁹). The hydrogen bromide-acetic acid method is superior to the preparation of epoxides from 1,2-diols via 1-O-sulfonate esters, because any contaminating 2-O-sulfonate ester will detract from the optical purity of the epoxide.¹⁰ The optical purities of the samples of (R)- and (S)-methyloxirane prepared as described were better than 98% according to complexation chromatography and ¹H NMR analysis with chiral shift reagent.^{11,12} Other procedures for preparing (R)-^{13,14} and (S)-methyloxirane have been described.¹⁵⁻¹⁷ These compounds are valuable starting materials for preparing a variety of optically active natural products (nonactin,¹⁸ sulcatol,¹⁹ recifeolide,²⁰ methyl-1,6-dioxaspiro[4.5]decane²¹), drugs (e.g. N-2-hydroxypropyl-6,7-benzomorphans²²) and for studies of stereoregular polymerizations.²³

1. Department of Chemistry and Molecular Sciences, University of Warwick, Coventry CV4 7AL, U.K. Present address: Department of Organic Chemistry, The University, Newcastle upon Tyne, NE1 7RU, U.K.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(+)-Propane-1,2-diol: 1,2-Propanediol, L- (8); 1,2-Propanediol, (S)- (9);
(4254-15-3)

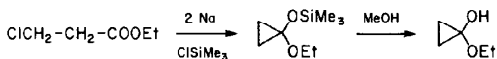
Ethyl L-(-)-lactate: Lactic acid, ethyl ester, L- (8); Propanoic acid,
2-hydroxy-, ethyl ester, (S)- (9); (687-47-8)

(S)-(-)-2-Acetoxy-1-bromopropane: 2-Propanol, 1-bromo-, acetate, (S)- (9);
(39968-99-5)

(S)-(-)-Methyloxirane: Oxirane, methyl-, (S)- (9); (16088-62-3)

CYCLOPROPANONE ETHYL HEMIACETAL FROM ETHYL 3-CHLOROPROPANOATE

(Cyclopropanol, 1-ethoxy-)



Submitted by J. Salaün and J. Marguerite.¹

Checked by Steven D. Young, Syun-ichi Kiyooka, and Clayton H. Heathcock.

1. Procedure

A. 1-Ethoxy-1-trimethylsiloxy-cyclopropane. A 1-L, three-necked, round-bottomed flask is fitted with an efficient mechanical stirrer (Note 1), reflux condenser provided with a calcium chloride tube, and a 500-mL pressure equalizing dropping funnel equipped at the top with a nitrogen inlet. The flask is flushed with dry nitrogen, and 500 mL of anhydrous toluene (Note 2) and 52.9 g (2.3 g-atom) of sodium cut in small pieces (Note 3) are introduced. The mixture is brought to reflux by means of a heating mantle and the sodium is finely pulverized by vigorous stirring. Heating and stirring are stopped (Note 4), and the mixture is allowed to cool to room temperature. Toluene is removed under nitrogen pressure by means of a double-ended needle and replaced by 500 mL of anhydrous diethyl ether (Notes 5, 6). At this point, 108.5 g (1 mol) of chlorotrimethylsilane (Note 7) is added to the flask. To the mixture, 136.58 g (1 mol) of ethyl 3-chloropropoate is added dropwise with stirring at a rate sufficient to maintain a gentle reflux

over a period of 3 hr (Note 8). When about 0.3 mol of chloro ester has been added, a deep-blue precipitate appears (Note 9). When the addition is over, the reaction mixture is heated at reflux for 30 min. The contents of the flask are cooled and filtered through a sintered glass funnel under a stream of dry nitrogen (Note 10). The precipitate is washed twice with 100 mL of anhydrous diethyl ether.

The colorless filtrate is transferred to a distilling flask and the solvent is distilled through a 25-cm vacuum-jacketed Vigreux column, and the residue is distilled under reduced pressure. After a small forerun (1-2 g), 1-ethoxy-1-trimethylsiloxy-cyclopropane is obtained at 43-45°C (12 mm) as a colorless liquid, 106 g (61%) (Note 11).

B. Cyclopropanone ethyl hemiacetal. Into a 500-mL Erlenmeyer flask fitted with a magnetic stirring bar is placed 250 mL of reagent grade methanol. Freshly distilled 1-ethoxy-1-trimethylsiloxy-cyclopropane (100 g, 0.56 mol) is added all at once to the methanol and the solution is stirred overnight (12 hr) at room temperature (Note 12). An aliquot (50 mL) of the solution is concentrated by slow evaporation of methanol with a rotary evaporator at room temperature (Note 13) and formation of the methanolysis product is checked by NMR examination of the residue (Note 14). When the reaction is complete (Note 15), the solution is concentrated by removal of the methanol (Note 16). Distillation of the residue through a 20-cm helix-packed, vacuum-insulated column under reduced pressure gives 52 g (89%) of 1-ethoxycyclopropanol, bp 60°C (20 mm) (Note 14, 17), which contains trace amounts of 1-methoxycyclopropanol (Notes 18, 19).

2. Notes

1. An efficient stirrer is used at a spinning rate sufficient to disperse the molten sodium into small beads of a diameter of approximately 0.1 mm. The checkers found it necessary to use a mechanical stirrer equipped with a nichrome wire "beater", rather than a Teflon paddle. If the sodium sand particles are too large, the final product will be contaminated with starting chloro ester, from which it is very difficult to separate.

2. Toluene is freshly distilled from phosphorus pentoxide into the reaction flask.

3. Sodium pieces are washed in dry pentane or toluene to remove oil.

4. It is essential that stirring be discontinued before cooling is begun to prevent the molten sodium from coalescing into one gigantic lump.

5. Diethyl ether is dried by molecular sieves and distilled from lithium aluminum hydride.

6. To remove the toluene completely, the finely divided sodium is washed under nitrogen with anhydrous diethyl ether (3 x 50 mL).

7. Chlorotrimethylsilane, obtained from Aldrich Chemical Co. or Prolabo (France), is distilled from quinoline or calcium hydride.

8. For the acyloin condensation of diesters it has been recommended that the diester and chlorotrimethylsilane be added together to the sodium dispersion;² no difference has been noted with our procedure.

9. The deep blue color seems to be indicative of a satisfactory reduction. When the color is yellow-green the yield is usually poor.

10. *Caution!* Because of the pyrophoric nature of finely divided alkali metal residues or production of free acid (HCl) from the chlorosilane, the products are sensitive to moisture. Unreacted sodium is destroyed by careful addition of ethanol to the residual solid.

11. The yield varies from 60 to 85%, bp 50-52°C (18 mm); 60-62°C (35 mm); 66-68°C (40 mm); the proton magnetic resonance spectrum (CCl_4 solution, HCCl_3 external reference) shows absorption at δ : 0.08 (s, 9 H), 0.70 (m, 4 H), 1.05 (t, 3 H, $J = 7.11$) and 3.55 (q, 2 H, $J = 7.11$); the infrared spectrum (CCl_4) exhibits absorption at 3090 and 3010 (cyclopropane), 1250, 845 and 758 cm^{-1} ($-\text{Si}[\text{CH}_3]_3$).

12. After the solution is stirred for 5-10 min, the clear solution becomes slightly turbid for a few minutes and then turns clear again. When these changes are not observed, methanolysis has not occurred.

13. If some 1-ethoxy-1-trimethylsilyloxycyclopropane is still present, it will be lost by too rapid evaporation of methanol.

14. The product has the following spectral properties: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ : 0.84 (s, 4 H), 1.18 (t, 3 H, $J = 7.11$), 3.73 (q, 2 H, $J = 7.11$) and 4.75 (m, 1 H).

15. Lack of NMR absorption around δ 0.08 shows that the trimethylsiloxy group has been completely removed.

16. If the reaction is not complete, as shown by the presence of a singlet around δ 0.08, a spatula-tip full of pyridinium *p*-toluenesulfonate³ is added and the mixture is stirred for 4 hr. Methanol is then removed, and the residue is dissolved in 200 mL of diethyl ether. The solution is washed with saturated sodium chloride until neutral, dried over anhydrous sodium sulfate, and concentrated. Addition of a drop of HCl, or of chlorotrimethylsilane is also effective to complete the reaction. Then, the hydrochloric acid is removed with methanol. (Thus, it is not necessary to wash with saturated sodium chloride until neutral).

17. The yield varies from 78 to 95%, bp 51°C (12 mm), 64°C (25 mm), 75°C (46 mm).

18. On standing with methanol at 25°C for 1 week, 65% of 1-ethoxycyclopropanol is converted into 1-methoxycyclopropanol; conversion appears to be complete after 15 days.⁴ The spectral properties of the 1-methoxycyclopropanol are: IR (CCl₄): 3600 and 3400 (hydroxyl), 3010 and 3090 cm⁻¹ (cyclopropyl); ¹H NMR (CCl₄) δ: 0.85 (s, 4 H) and 3.40 (s, 3 H).

19. Cyclopropanone hemiacetal can be kept unaltered for several months at 0°C in the refrigerator. On heating above 100°C or on standing in acidic solvents, it undergoes ring opening to give ethyl propionate.

3. Discussion

Cyclopropanone ethyl hemiacetal was first synthesized by the reaction of ketene and diazomethane in ether at -78°C in the presence of ethanol.⁴ The yield is low (43%) and the reaction is hazardous, especially when a large-scale reaction is required. The method described in this procedure for the preparation of cyclopropanone ethyl hemiacetal from ethyl 3-chloropropanoate is an adaptation of that described previously;⁵ the procedure described for the synthesis of 1-ethoxy-1-trimethylsiloxycyclopropane is patterned after the method reported by Rühlmann.⁶

Cyclopropanone ethyl hemiacetal is a molecule of considerable interest since its reactions appear to involve the formation of the labile cyclopropanone.⁷ It readily undergoes nucleophilic addition of Grignard reagents,^{4,5} azides,⁴ and amines⁸ to provide 1-substituted cyclopropanols in high yields. It has been reported that upon treatment with an equimolar amount of methylmagnesium iodide, the cyclopropanone ethyl hemiacetal is converted into iodomagnesium 1-ethoxycyclopropylate,⁹ which can react with hydrides, organometallic reagents, cyanide carbanion, and phosphorus ylides¹⁰

to provide useful synthons. Very recently, the preparation of some challenging 2,3-disubstituted cyclopentanones including a total synthesis of the 11-deoxyprostaglandin, has been reported from the cyclopropanone hemiacetal.¹¹ The ready availability of this compound should lead to other synthetic applications. For a recent review dealing with the chemistry of the cyclopropanone hemiacetals, see reference 12.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclopropanone ethyl hemiacetal: Cyclopropanol, 1-ethoxy- (8,9); (13837-45-1)

1-Ethoxy-1-trimethylsiloxy-cyclopropane: Silane, [(1-ethoxycyclopropyl)oxy]-trimethyl- (8,9); (27374-25-0)

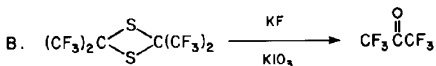
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Ethyl 3-chloropropanoate: Propionic acid, 3-chloro-, ethyl ester (8);

Propanoic acid, 3-chloro-, ethyl ester (9); (623-71-2)

HEXAFLUOROACETONE

(2-Propanone, 1,1,1,3,3,3-hexafluoro-)



Submitted by Michael Van Der Puy and Louis G. Anello.¹

Checked by Evan D. Laganis and Bruce E. Smart.

Caution! Hexafluoroacetone and its precursor are toxic. Both procedures should be conducted in an efficient hood.

1. Procedure

A. *2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane*. A 500-mL, three-necked flask is fitted with a good magnetic stirring bar, thermometer, water-cooled condenser, and a fritted gas inlet tube (Note 1). The outlet of the condenser is attached to a tared -78°C cold trap and the inlet tube is connected via flexible tubing to a graduated -78°C cold trap into which 60 mL (96 g, 0.64 mol) of hexafluoropropene has been condensed under nitrogen. The flask is charged with 3 g of potassium fluoride and is flamed gently under vacuum. The apparatus is cooled while purging with nitrogen. Sulfur (23 g, 0.72 mol) and 200 mL of dry dimethylformamide are then added (Note 2). The reaction mixture is heated to 40-45°C with stirring. The heat source is

removed, the stopcock on the trap containing the hexafluoropropene is opened, and the trap is gently thawed. The rate of hexafluoropropene bubbling into the reaction mixture is adjusted to about 0.6 mL (1 g)/min by cooling or warming the trap containing the hexafluoropropene (Notes 3, 4 and 5). When all of the hexafluoropropene has been added, the reaction mixture is cooled to -20°C to -30°C and quickly filtered under suction (Note 6). The filtercake is transferred to an Erlenmeyer flask and is allowed to melt. Water (50 mL) is added, and the mixture is filtered. The lower liquid phase is separated, washed with 50 mL of water, and distilled through a 20-cm Vigreux column at atmospheric pressure to give 93.0-99.4 g (80-85%) of product, bp 106-108°C (Note 7).

B. Hexafluoroacetone. A 1-L, three-necked flask is fitted with a sealed mechanical stirrer, thermometer, and condenser. A -78°C glass trap is attached to the condenser via flexible tubing. While the system is purged with nitrogen, 3 g of potassium fluoride is added and the flask and potassium fluoride are flame dried (Note 8). After the flask has cooled, 300 mL of dry dimethylformamide, 80 g (0.374 mol) of powdered potassium iodate and 60 g (0.165 mol) of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane are added (Note 9). The stirrer and water condenser are started and the reaction mixture is heated over a 45-min period to 149°C and is kept at 149°C for an additional 15 min. The heat source is then removed, and a slow stream of nitrogen is used to flush any remaining product gas into the cold trap (Note 8). The condensate is transferred under vacuum to a tared, evacuated gas cylinder (Note 10). The cylinder contains 37.0-39.9 g (68-73%) of material (Note 11). This material is distilled to give 35.0-37.6 g (64-69%) of pure product, bp -28°C [11² bp -27°C] (Note 12).

2. Notes

1. The checkers dried the glassware overnight at 150°C in an oven and assembled it hot under a nitrogen purge.

2. The checkers obtained potassium fluoride, potassium iodate, dimethylformamide (reagent grades), and sulfur (sublimed) from Fisher Scientific Co. The submitters purchased hexafluoropropene from PCR Research Chemicals, Inc.; the checkers used hexafluoropropene from E. I. du Pont de Nemours & Company, Inc. The potassium fluoride was pre-dried overnight in a vacuum oven at 110°C. The sulfur was dried in a vacuum desiccator and the dimethylformamide was distilled from P_2O_5 prior to use.

3. The mixture of dimethylformamide, sulfur and potassium fluoride turns brown prior to the addition of hexafluoropropene, which quickly brings the color back to bright yellow. The submitters report that the reaction mixture will turn blue or green prior to the addition of hexafluoropropene, if the dimethylformamide is dry (less than about 0.05% water).

4. The reaction is moderately exothermic. The temperature rises to about 55°C and remains there as the reaction proceeds.

5. With good stirring, the reaction proceeds as fast as the hexafluoropropene is added. The dry-ice trap attached to the condenser should be checked periodically, however. When the required amount of hexafluoropropene is added, little or no undissolved sulfur remains.

6. 2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane melts at 24°C. Thus, this operation must be done quickly to minimize product loss.

7. The product is more than 99% pure by GLPC (6 ft x 1/8 in 20% FS-1265 on 60/80 Gaschrome R, 50-200°C) and by ^{19}F NMR ($CDCl_3$) δ : -73.3 (s). The submitters report that they obtained 78-90 g of 98% pure product, bp 110°C.

8. The nitrogen initially should come from the cold trap, itself cooled under a nitrogen flush. At the end of the reaction, the flow of nitrogen should be reversed. This can be done by replacing the thermometer with a gas inlet tube.

9. The submitters report that a ratio of KIO_3 to 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane of 2.26 is near the optimum since a ratio of 2.5 did not increase the yield, whereas a ratio of 2.0 gave 5-10% lower yields.

10. This transfer is best done on a vacuum manifold system equipped with a manometer. The trap and a stainless steel cylinder of 100-300 mL capacity are attached via vacuum tubing to the manifold system, cooled in liquid nitrogen baths, and evacuated to 0.5-1 mm. The system is closed, the trap is removed from its cold bath and is slowly thawed. The volatile material in the trap is transferred to and condensed in the cylinder at such a rate that no positive pressure builds up in the closed system.

11. The submitters report collecting 45-50 g of product (98% pure or better by GLPC on a 10 ft x 1/8 in Porapak P column) in the cold trap attached to reaction vessel. The checkers found that the trap contained relatively non-volatile material, principally dimethylformamide, in addition to the desired product.

12. The checkers used a 30-cm jacketed, low temperature spinning band column for this distillation. The IR spectrum of the distilled product is identical to that of an authentic sample; IR (vapor) cm^{-1} : 1806 (C=O).

3. Discussion

Earlier methods of preparing 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (hexafluorothioacetone dimer, HFTA dimer) include the reaction of hexafluoropropene (HFP) and sulfur over a carbon bed at 425°C,³ and the reaction of HFP and sulfur in tetramethylene sulfone at 120°C in the presence of potassium fluoride (autoclave).⁴ Dimethylformamide appears to be a far superior solvent for this reaction, permitting the use of atmospheric pressure and modest temperatures, as well as affording a cleaner product.

The generation of hexafluoroacetone (HFA) from HFTA dimer has been accomplished by the hot-tube oxidation with nitric oxide at 650°C (high temperature converts dimer into monomer).⁵ The present method uses the more convenient interconversion of dimer to monomer effected by potassium fluoride in dimethylformamide. This permits many reactions to be conducted on the very reactive monomer without actually isolating it.

For occasional laboratory synthesis of HFA, the present method offers distinct advantages of convenience (cost, work-up, standard equipment) over other known methods. These include the epoxidation of HFP followed by isomerization of the epoxide to HFA,⁶ the high temperature halogen exchange of hexachloroacetone with Cr^{+3}/HF ,⁷ and permanganate oxidation of the extraordinarily toxic perfluoroisobutylene.⁸

Hexafluoroacetone is a reactive electrophile. It reacts with activated aromatic compounds (e.g., phenol), and can be condensed with olefins, dienes, ketenes, and acetylenes. It forms adducts with many compounds containing active hydrogen (e.g., H_2O or HCN). Reduction of HFA with NaBH_4 or LiAlH_4 affords the useful solvent hexafluoroisopropyl alcohol. The industrial importance of HFA arises largely from its use in polymers and as an intermediate in monomer synthesis.⁹

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9. References can be found in Ref. 2 and in the review; Krespan, C. G.; Middleton, W. J. *Fluorine Chem. Rev.* **1967**, *1*, 145.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Hexafluoroacetone: 2-Propanone, 1,1,1,3,3,3-hexafluoro- (8,9); (684-16-2)

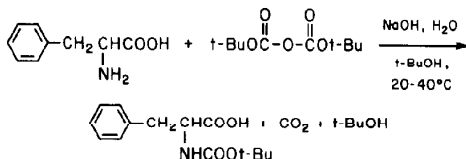
2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane: 1,3-Dithietane, 2,2,4,4-tetrakis(trifluoromethyl)- (8,9); (791-50-4)

Hexafluoropropene: Propene, hexafluoro- (8); 1-Propene, 1,1,2,3,3,3-hexafluoro- (9); (116-15-4)

tert-BUTOXYCARBOXYLATION OF AMINO ACIDS AND THEIR DERIVATIVES:

N-tert-BUTOXYCARBOXYL-L-PHENYLALANINE

(L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-)



Submitted by Oskar Keller, Walter E. Keller, Gert van Look,
and Gernot Wersin.¹

Checked by Thomas von Geldern, Mark A. Sanner,
and Clayton H. Heathcock.

1. Procedure

A 4-L, four-necked, round-bottomed flask, equipped with an efficient stirrer, a dropping funnel, reflux condenser, and thermometer is charged with a solution of 44 g (1.1 mol) of sodium hydroxide in 1.1 L of water. Stirring is initiated and 165.2 g (1 mol) of L-phenylalanine (Note 1) is added at ambient temperature, and then diluted with 750 mL of tert-butyl alcohol (Note 2). To the well-stirred, clear solution (Note 3) is added dropwise within 1 hr, 223 g (1 mol) of di-tert-butyl dicarbonate (Note 4). A white precipitate appears during addition of the di-tert-butyl dicarbonate. After a short induction period, the temperature rises to about 30-35°C. The reaction is brought to completion by further stirring overnight at room temperature. At

this time, the clear solution will have reached a pH of 7.5-8.5. The reaction mixture is extracted two times with 250 mL of pentane and the organic phase is extracted three times with 100 mL of saturated aqueous sodium bicarbonate solution. The combined aqueous layers are acidified to pH 1-1.5 by careful addition of a solution of 224 g (1.65 mol) of potassium hydrogen sulfate in 1.5 L of water (Note 5). The acidification is accompanied by copious evolution of carbon dioxide. The turbid reaction mixture is then extracted with four 400-mL portions of ethyl ether (Note 6). The combined organic layers are washed two times with 200 mL of water, dried over anhydrous sodium sulfate or magnesium sulfate, and filtered. The solvent is removed under reduced pressure using a rotary evaporator at a bath temperature not exceeding 30°C (Note 7). The yellowish oil that remains is treated with 150 mL of hexane and allowed to stand overnight (Note 8). Within 1 day the following portions of hexane are added with stirring to the partially crystallized product: 2 x 50 mL, 4 x 100 mL, and 1 x 200 mL. The solution is placed in a refrigerator overnight; the white precipitate is collected on a Buchner funnel and washed with cold pentane. The solid is dried under reduced pressure at ambient temperature to constant weight to give a first crop. The mother liquor is evaporated to dryness leaving a yellowish oil, which is treated in the same manner as described above, giving a second crop (Note 9). The total yield of pure white N-tert-butoxycarbonyl-L-phenylalanine is 207-230 g (78-87%), mp 86-88°C, $[\alpha]_D^{20} + 25.5^\circ$ (ethanol, c 1.0) (Note 10).

2. Notes

1. L-Phenylalanine puriss. from Fluka AG or Tridom Chemical Inc. was used.
2. All of the solvents and reagents used were of purum grade and obtained from Fluka AG.
3. At this stage, the reaction mixture has a pH of 12-12.5.
4. Di-tert-butyl dicarbonate can be prepared according to Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Org. Synth.* **1977**, *57*, 45-60 or purchased from Fluka AG. Di-tert-butyl dicarbonate melts at 22-24°C; this compound can be liquified by immersing the reagent bottle in a water bath with a maximum temperature of 35°C. Commercial material is 97-98% pure; a total of 223 g must be employed.
5. It is recommended that acidification be carried out at a temperature of 0-5°C.
6. Ethyl or isopropyl acetate may also be used as extraction solvents for less lipophilic N-tert-butoxycarbonyl amino acids.
7. Evaporation should be performed first at 10-20 mm, then at a pressure less than 1 mm in order to remove the tert-butyl alcohol completely. Remaining small quantities of tert-butyl alcohol lead to difficulty in crystallization.
8. Seeding or scratching with a glass rod helps to induce crystallization.
9. Normally it is not worthwhile to isolate a third crop, which is of lower purity.
10. N-tert-Butoxycarbonyl-L-phenylalanine prepared by this method is obtained in a very pure state. Thin layer chromatography shows a single spot

and a content of less than 0.05% free amino acid. Acylation of lipophilic amino acids with excess di-tert-butyl dicarbonate may result to some extent in formation of the corresponding N-tert-butoxycarbonyl dipeptide.

3. Discussion

In recent years the tert-butoxycarbonyl (BOC) group has achieved a leading role as a protective group for the amino moiety of amino acids in peptide synthesis.² At one time the most widely used tert-butoxycarbonylating agent was the hazardous³ and toxic tert-butyl azidoformate.⁴ Di-tert-butyl dicarbonate⁵ is a highly reactive and safe reagent of the "ready-to-use" type which reacts under mild conditions with amino acids,^{5a,6a-i} peptides,^{6j-l} hydrazine and its derivatives,⁷ amines,^{8a-g} and CH-acidic compounds^{8h} in aqueous organic solvent mixtures to form pure derivatives in very good yields. Acylation with di-tert-butyl dicarbonate proceeds normally without strict pH control. The procedure given here demonstrates a suitable large-scale and safe preparation of an N-tert-butoxycarbonylamino acid with extremely simple experimental operations. Table I shows some other BOC-amino acids and derivatives prepared by this method. N-tert-Butoxycarbonyl-L-phenylalanine has also been prepared by acylation of L-phenylalanine with other tert-butoxycarbonylating agents: tert-butyl 4-nitrophenyl carbonate,⁹ tert-butyl azidoformate,¹⁰ tert-butyl 2,4,5-trichlorophenyl carbonate,¹¹ tert-butyl pentachlorophenyl carbonate,¹² tert-butyl 8-quinolyl carbonate,¹³ tert-butyl chloroformate,¹⁴ tert-butyl fluoroformate,¹⁵ tert-butyl phenyl carbonate,¹⁶ N-tert-butoxycarbonyl-1H-1,2,4-triazole,¹⁷ tert-butyl 4,6-dimethylpyrimidyl-2-thiol carbonate,¹⁸ N-tert-butoxycarbonyloxyimino-2-phenylacetonitrile,¹⁹ tert-butyl α -methoxyvinyl carbonate,²⁰ tert-butyl minocarbonate (tert-butoxycarbonyloxyamine).²¹

Table I

BOC-AMINO ACIDS PREPARED BY ACYLATION WITH DI-tert-BUTYL DICARBONATE

BOC-Amino Acids ^a	Solvent ^b	Base	Time (hr) ^c	Yield, %	mp, °C	$[\alpha]_D^{20}$	Remarks
BOC-Ala-OH	A	NaOH	16	92-94	82-83	-25.5 (acetic acid, c 2.0)	pH 8.0 ²
BOC-B-Ala-OH	A	NaOH	16	85-86	76-77		
BOC-Arç-OH	B	--	15	88	159-160 (dec)	- 6.8 (acetic acid, c 1.0)	extraction with n-butyl alcohol
BOC-Arç(NO ₂)-OH ^d	B	NaOH	15	82	107	-22.0 (pyridine, c 2.0)	pH 8.5 ²
BOC-Asn-OH	C	NaOH	18	80-81	176 (dec)	- 7.2 (dimethylformamide, c 2.0)	5 hr, 45-50°C
BOC-Asp(OBzl)-OH	A	NaOH	16	81-89	101-102	-19.7 (dimethylformamide, c 2.0)	pH 8.0 ²
BOC-Cys(Bzl)-OH	B	NaOH	15	65	86-87	-43.4 (acetic acid, c 1.0)	
(BOC-Cys-OH) ₂	D	NaOH	16	85	143-145 (dec)	-115.6 (acetic acid, c 2.0)	
BOC-Gln-OH	E	NaOH	18	76	125 (dec)	- 3.4 (ethanol, c 2.0)	pH 8.0 ^e
BOC-Glu(OBzl)-OH ^f	B	NaOH	15	86	142-143	+13.2 (methanol, c 1.0)	pH 8.5-9 ^e
BOC-Gly-OH	A	NaOH	16	96	87-88		
BOC-His(BOC)-OH	A	KHCO ₃	18	75	170 (dec)	+19.5 (chloroform, c 2.0)	
BOC-Ile-OH	A	NaOH	16	78	69-71	+ 2.8 (acetic acid, c 2.0)	
BOC-Leu-OH ^g	A	NaOH	18	96	85-87	-24.7 (acetic acid, c 2.0)	
BOC-Lys(BOC)-OH ^f	A	NaOH	16	82	138-139	+ 6.1 (dimethylformamide, c 1.5)	
BOC-Lys(CBZ)-OH	A	NaOH	18	96	oil		
BOC-Met-OH	A	NaOH	18	60 ^h	50-51	-22.8 (methanol, c 1.3)	
BOC-Met-OH ^f	A	NaOH	18	85	139-140	+18.2 (ethanol, c 2.0)	
BOC-Pro-OH	A	NaOH	12	95	134-135	-60.6 (acetic acid, c 2.0)	

Table I (cont.)

BOC-Amino Acids ^a	Solvent ^b	Base	Time (hr) ^c	Yield, %	mp, °C	$[\alpha]_D^{20}$	Remarks
BOC-Ser-OH	A	NaOH	16	66-32	86-88	- 3.6 (acetic acid, c 2.0)	pH 8.5-9 ^e
BOC-Ser(Bzl)-OH	B	NaOH	16	90	62-63	+19.2 (80% ethanol, c 2.0)	pH 8.5-9 ^e
BOC-Thr-OH	A	NaOH	16	85	71-73	- 8.2 (acetic acid, c 1.0)	
BOC-Trp-OH ⁱ	A	NaOH	16	96	137-138 (dec)	-18.2 (dimethylformamide, c 1.0)	
BOC-Trp-(FOR)-OH ^f	F	Et ₃ N	48	61	158-159 ^k	+36.0 (ethanol, c 2.0)	
BOC-Tyr-OH	A	NaOH ^l	24	75	137 ^m	+ 2.6 (acetic acid, c 1.0)	
BOC-Tyr-OH ^f	A	NaOH ^l	24	84	216	+ 2.6 (acetic acid, c 1.0)	
BOC-Tyr(Bzl)-OH	B	NaOH	18	70	110-111	+27.6 (ethanol, c 1.0)	pH 10.4 ^e
BOC-Tyr(2,6-Cl ₂ - Bzl)-OH	A	NaOH	24	48	104 (dec)	+20.6 (ethanol, c 2.0)	
BOC-Val-OH	A	NaOH	16	85	76-78	- 7.5 (acetic acid, c 1.0)	

^aThe amino acids used, with the exception of β -alanine and glycine, were of L-configuration. The abbreviations used for amino acids and their protecting substituents concor with E. Wünsch.²

^bSolvent systems: A: tert-butyl alcohol/water; B: dioxane/water; C: dimethylformamide/water; D: methanol/water; E: acetonitrile/water; F: dimethylformamide.

^cThe reaction was generally carried out at room temperature after the exothermic starting period had subsided. Progress of the reaction was monitored by thin layer chromatography. Reaction times are not optimized.

^dCrystallizes with ~15% solvent (ethyl acetate).

^epH control is necessary.

^fDicyclohexylamine salt.

Table I (cont.)

³Monohydrate.

^hThe yield of crude semi-solid product was 90%. This material was pulverized by efficient stirring in hexane over a period of 24 hr at -10°C under strictly anhydrous conditions.

ⁱCrystallizes with ~4% solvent (ethyl acetate).

^kDecomposes below 130°C if heated rapidly.

^lTwo equivalents of base were employed.

^mResolidifies at 138°C and does not melt below 300°C.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

L-Phenylalanine (8,9); (63-91-2)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

Dicarboxic acid, bis(1,1-dimethylethyl) ester (9); (24424-99-5)

Ethyl ether (8); Ethane, 1,1'-oxybis- (9); (60-29-7)

Alanine, N-carboxy-3-phenyl-N-tert-butyl ester, L- (8); L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]- (9); (13734-34-4)

Carbonic acid, tert-butyl p-nitrophenyl ester (8); Carbonic acid, 1,1-dimethylethyl 4-nitrophenyl ester (9); (13303-10-1)

Formic acid, azido-, tert-butyl ester (8); Carbonazidic acid, 1,1-dimethylethyl ester (9); (1070-19-5)

Carbonic acid, tert-butyl 2,4,5-trichlorophenyl ester (8); Carbonic acid, 1,1-dimethylethyl 2,4,5-trichlorophenyl ester (9); (16965-08-5)

Carbonic acid, tert-butyl pentachlorophenyl ester (8); Carbonic acid, 1,1-dimethylethyl pentachlorophenyl ester (9); (18942-25-1)

Carbonic acid, 1,1-dimethylethyl 8-quinolinylnyl ester (9); (18595-55-6)

Formic acid, chloro-, tert-butyl ester (8); Carbonochloridic acid, 1,1-dimethylethyl ester (9); (24608-52-4)

Formic acid, fluoro-, tert-butyl ester (8); Carbonofluoridic acid, 1,1-dimethylethyl ester (9); (18595-34-1)

Carbonic acid, tert-butyl phenyl ester (8); Carbonic acid, 1,1-dimethylethyl phenyl ester (9); (6627-89-0)

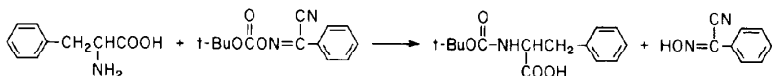
1H-1,2,4-Triazole-1-carboxylic acid, 1,1-dimethylethyl ester (9); (41864-24-8)

Carbonothioic acid, O-(1,1-dimethylethyl) S-(4,6-dimethyl-2-pyrimidinyl) ester (9); (41840-28-2)

Benzeneacetonitrile, α -[[[(1,1-dimethylethoxy)carbonyl]oxy]imino]- (9); (58632-95-4)

tert-BUTOXYCARBONYL-L-PHENYLALANINE

(L-Phenylalanine, N[(1,1-dimethylethoxy)carbonyl])-)



Submitted by William J. Paleveda, Frederick W. Holly, and Daniel F. Veber.¹

Checked by Mark A. Sanner, Thomas von Geldern, and Clayton H. Heathcock.

1. Procedure

To a stirred mixture of 16.51 g (0.1 mol) of L-phenylalanine in 60 mL of water and 60 mL of peroxide-free dioxane (Note 1) is added 21 mL of triethylamine. To the resulting solution is added 27.1 g (0.11 mol) of 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Note 2). Solution is obtained during the first hour of stirring. After 3 hr (Note 3) the solution is diluted with 150 mL of water. The resulting turbid solution is extracted with at least four 200-mL portions of ethyl ether (Note 4). The aqueous layer is then acidified to pH 2.5 with cold 2.5 N hydrochloric acid to yield an oily layer. The mixture is extracted with three 100-mL portions of methylene chloride. The combined organic extracts are dried with anhydrous sodium sulfate. After filtration of the sodium sulfate, the filtrate is evaporated under reduced pressure at a bath temperature of 30°C. Hexane is added to the thick oil to turbidity. Crystallization occurs after cooling and stirring the mixture for a short time. More hexane is added in portions until no further

crystallization occurs. A total of 200 mL of hexane is required. The mixture is allowed to stand for 1 hr. The white crystalline solid is collected by filtration, washed with three 100-mL portions of hexane, and dried under reduced pressure to yield 21.4-22.0 g (80-83%) of tert-butoxycarbonyl-L-phenylalanine, mp 86-88°C, $[\alpha]_D^{20}$ -3.6° (HOAc, c 1), $[\alpha]_{546}^{20}$ 29.9° [EtOH, c 1) (Note 5).

2. Notes

1. Peroxides are removed from dioxane by passage through an alumina column.²

2. 2-(tert-Butoxycarbonyloxyimino)-2-phenylacetonitrile is obtained from Aldrich Chemical Company, Inc., under the trademark "BOC-ON".

3. The reaction is allowed to continue until TLC (Whatman KIF, ethyl acetate-pyridine-acetic acid-water, 10:5:1:3) shows that the unprotected amino acid (R_f 0.4) is no longer present, as evidenced by negative ninhydrin spray.

4. It is imperative that all of the by product is removed at this point; otherwise it will contaminate the product, making crystallization difficult. Each ether extract is spotted on a Whatman KIF plate and the plate viewed under UV light to ascertain that all of the by-product has been extracted. The checkers found that six or seven ether extractions were required to remove the by-product completely.

5. The literature gives melting points ranging from 79-80°C to 84-86°C the optical rotation is reported as $[\alpha]_D^{25}$ -0.8° (HOAc, c 4.957), $[\alpha]_D^{20}$ -4.8 (HOAc, c 1), $[\alpha]_{546}^{20}$ 30° (EtOH, c 1).

The spectral properties of tert-butoxycarbonyl-L-phenylalanine are as follows: ^1H NMR (CD_3OD) δ : 1.36 (s, 9 H, t-butyl), 2.87 (dd, 1 H, $J = 14.9$, H_β), 3.16 (dd, 1 H, $J = 14.6$, H_β), 4.36 (dd, 1 H, $J = 9.6$, H_α), 7.26 (s, 5 H, phenyl). In CDCl_3 solution, both carbamate rotamers may be seen in the ^1H NMR spectrum.

3. Discussion

Various reagents have been used for the introduction of the tert-butoxycarbonyl group, including tert-butyl p-nitrophenyl carbonate,³ tert-butyl azidoformate⁴ (no longer commercially available because of its toxic and potentially explosive nature), tert-butyl 2,4,5-trichlorophenyl carbonate,⁵ di-tert-butyl dicarbonate,⁶ and the reagent described herein, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile.⁷ Using the same reagent, the crystalline BOC derivatives of the following amino acids have been prepared in these laboratories in the indicated yields: 7-aminoheptanoic acid (88%), DL-tyrosine (96%), 6-fluoro-DL-tryptophan (87%), 5-methyl-DL-tryptophan (95%), 5-bromo-DL-tryptophan (94%), 5-methoxy-DL-tryptophan (67%), 1-methyl-DL-tryptophan (82%), and 5-fluoro-DL-tryptophan (62%).

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

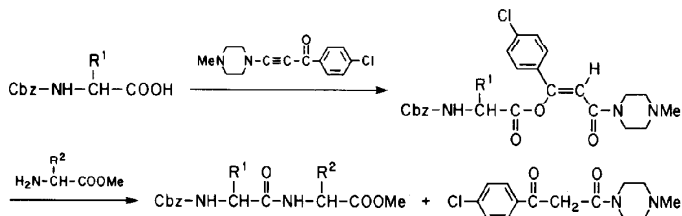
tert-Butoxycarbonyl-L-phenylalanine: L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]- (9); (13/34-34-4)

L-Phenylalanine (8,9); (63-91-2)

2-(tert-Butoxycarbonyloxyimino)-2-phenylacetonitrile; Aldrich "BOC-ON":

Benzonacetonitrile, α -[[[(1,1-dimethylethoxy)carbonyl]oxy]imino]- (9); (58632-95-3)

PEPTIDE SYNTHESIS USING 1-(4-CHLOROPHENYL)-3-(4'-METHYL-1'-PIPERAZINYL)-
2-PROPYN-1-ONE AS REAGENT: BENZYLOXYCARBONYL-L-ALANYL-L-CYSTEINE
METHYL ESTER AND BENZYLOXYCARBONYL-L-ASPARTYL-(*tert*-BUTYL ESTER)-L-
PHENYLALANYL-L-VALINE METHYL ESTER



Submitted by H. P. Fahrni, U. Lienhard and M. Neuenschwander.¹

Checked by David R. Bolin and Gabriel Saucy.

1. Procedure

A. *Benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester.* A round-bottomed, three-necked, 100-mL flask is equipped with a magnetic stirring bar, 10-mL dropping funnel, thermometer and nitrogen bubbler (Note 1). The apparatus is flushed with dry nitrogen and then charged with 446.5 mg (0.002 mol) of benzyloxycarbonyl-L-alanine in 10 mL of dry dichloromethane. The mixture is stirred until solution is complete and then cooled to 0°C. Within 20 min a solution of 525.5 mg (0.002 mol) of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one (Note 2) in 5 mL of dry dichloromethane is added. Stirring is continued for 1 hr at 0°C and for a further hour at room

temperature (t_1). The mixture is cooled again to 0°C and a suspension of 343.3 mg (0.002 mol) of L-cysteine methyl ester hydrochloride is quickly added, followed by a solution of 202.3 mg (0.002 mol) of N-methylmorpholine in 5 mL of dry dichloromethane. While the nitrogen atmosphere is maintained, the mixture is allowed to warm up and is stirred for 12 hr (t_2) at room temperature. The solvent is removed by rotary evaporation, and the residue is shaken intensively with 30 mL of ethyl acetate and 10 mL of water. The organic layer is extracted two times with 10-mL portions of aqueous 10% citric acid and once with 5 mL of 1 N sodium hydrogen carbonate. The organic phase is dried over sodium sulfate. The solvent is removed by rotary evaporation to leave 647 mg (95%) of the crude pale yellow dipeptide. Recrystallization from ethyl acetate provides 551 mg (81%) of colorless crystals of benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester, mp 115-117°C; $[\alpha]_D^{20}$ -26.4° (CH₃OH, c 1.29), (Note 3).

B. *Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester*. A round-bottomed, three-necked, 100-mL flask is equipped with a 10-mL dropping funnel, thermometer, magnetic stirring bar and a nitrogen bubbler. The flask is flushed with dry nitrogen and then charged with a solution of 941.1 mg (0.002 mol) of benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine (Note 4) in 10 mL of dry dichloromethane. The flask is maintained under a dry nitrogen atmosphere and cooled to 0°C with an ice/salt bath. The mixture is stirred and a solution of 525.5 mg (0.002 mol) of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one (Note 2) in 5 mL of dry dichloromethane is added during a period of 20 min. Stirring is continued for 1 hr at 0°C and for 5 hr at room temperature (t_1). The mixture is again cooled to 0°C and a suspension of 335.3 mg (0.002 mol) of L-valine methyl ester hydrochloride and 202.3 mg (0.002 mol) of N-methylmorpholine in 5

mL of dichloromethane is added. After 30 min the reaction mixture is allowed to warm up and is stirred overnight (18 hr; t_2) at room temperature. The solvent is removed by rotary evaporation and the residue is shaken intensively with 40 mL of ethyl acetate and 10 mL of water. The organic layer is extracted twice with 10-mL portions of aqueous 10% citric acid and once with 5 mL of 1 N sodium hydrogen carbonate.

The organic phase is dried over sodium sulfate, and solvent is removed by rotary evaporation to leave 1132 mg (97%) of the crude pale-yellow tripeptide. For further purification the crude product is dissolved in ethyl acetate, treated with some activated carbon and filtered through Celite. Removal of the solvent and crystallization from ethyl acetate/ether/petroleum ether (ca. 2:1:1) yields 993 mg (85%) of colorless crystals of benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester; mp 119-120°C (Note 5).

2. Notes

1. Cysteine derivatives are oxidized to cystine by oxygen. The nitrogen atmosphere for preparation of Cbz-alanycysteine methyl ester is therefore indispensable and is recommended for other cases as well.

2. This reagent is available from Fluka Chemical Corp.

3. The literature² value is $[\alpha]_D^{20} -26.5^\circ$ (CH_3OH , c 1.27). The reported² mp is 116.5-118°C.

4. Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine dicyclohexylamine salt was conveniently prepared by standard procedures.³ The salt was dissolved in ethyl acetate and extracted three times with aqueous 10% citric acid, and once with water. The organic phase was dried and solvent was removed to leave the dipeptide as an oil.

5. The product has the following physical properties: Specific rotation: $[\alpha]_D^{20} -36.5^\circ$ (C_2H_5OH , c 2); IR (KBr), cm^{-1} : 3285, 1732, 1691, 1640, 1531, 1367, 1229, 1158, 1050, 746, /01; 1H NMR (100 MHz, $CDCl_3$), δ : 7.57 (s, 5 H), 7.21 (s, 5 H), 7.02 (d, 1 H, $J = 8$), 6.28 (d, 1 H, $J = 8$), 5.78 (d, 1 H, $J = 8$), 5.11 (s, 2 H), 4.8-4.3 (m, in total 3 H), 3.71 (s, 3 H), 3.08 (d, 1 H, $J = 8$), 2.86 (d or d, 1 H, $J = 17$, $J' = 5$), 2.02 (d or d, 1 H, $J = 17$, $J' = 6$), 2.3-1.8 (m, 2 H), 1.41 (s, 9 H), 0.84 (d, 3 H, $J = 7$), 0.81 (d, 3 H, $J = 7$).

3. Discussion

This procedure illustrates the use of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one⁴ as a reagent for peptide synthesis.⁵ The same method also gives amides in excellent yields.⁶

The preparation of Cbz-L-alanylcysteine methyl ester shows the advantage of using, as the amine component, an amino acid with an unprotected sulfhydryl moiety. No problems were encountered with the use of amino acid derivatives with unprotected hydroxyl or sulfhydryl groups as either the amine⁵ or carboxyl component.⁷ This procedure is based on the pronounced selective reactivity of the enol ester, which is generated by the addition of carboxylic acids to "push-pull acetylenes." Generally, the yields of peptides are good and a broad variety of solvents (e.g., dichloromethane, tetrahydrofuran, acetonitrile, dimethylformamide) may be used, depending on the solubility of the coupling components. It is also possible to change the solvent after the activation step or to isolate the activated components. However, normally this is neither necessary nor recommended. Purification of the reaction mixture is simple, since the piperazine by-product is conveniently extracted with an acidic water phase.

The following peptides and further examples have been prepared⁵ by this procedure:

<u>Peptide</u>	<u>t₁^a</u>	<u>t₂^b</u>	<u>Yield^c</u>
Cbz-L-Ala-Gly-OMe	2 ^d	12	91%
Cbz-L-Ala-L-Val-OMe	2 ^d	24	84%
Cbz-L-Ala-L-Phe-OMe	2 ^d	18	88%
Cbz-Gly-L-Phe-Gly-OEt	2	12	90%
Cbz-L-Asp(O-t-Bu)-L-Phe-L-Val-OMe	6	18	85%
Cbz-L-Ile-L-Ile-OBzl	18	24	75%
Cbz-L-Ala-L-Ser-OMe	2 ^d	72	90%
Cbz-L-Ala-L-Tyr-OMe	2 ^d	72	91%
Cbz-L-Ala-L-Cys-OMe	2 ^d	12	81%
Cbz-L-Ala-L-Met-OMe	2 ^d	15	85%
Cbz-L-Ser-Gly-OEt	2	24	81%

^at₁: time for activation of the carboxylic component (see procedures).

^bt₂: time for coupling (see procedures). ^cYield of pure recrystallized product. ^dStirring 1 hr at 0°C, then 1 hr at 20°C.

During our experiments no side reactions were detected. This is in contrast to peptide synthesis with isoxazolium salts,⁸ where some side reactions, one leading to a diacyl amino compound, were observed.⁹ In most cases, these side reactions are due to a secondary amino group in the reagent which is impossible in the case of push-pull-acetylenes.

Compared with ynamines, which have also been applied to peptide synthesis,¹⁰ push-pull-acetylenes are much more selective. They do not show the side reactions observed with ynamines,¹¹ and the yields are not markedly influenced by the sequence of addition of compounds in the activation step or by excess of acetylene reagent.

A crucial point in peptide synthesis is racemization of the activated amino acid. Three different tests were made to evaluate the degree of racemization. Using the Anderson test-peptide¹² Cbz-Gly-Phe-Gly-OEt, no racemization could be detected when the peptide was prepared in dichloromethane, acetonitrile or tetrahydrofuran. This means racemization is below the detection limit of 1%. Benzylleucylglycine ethyl ester is used in the very sensitive Young test.¹³ In this test, designed to exaggerate racemization, we found 5% of racemate, when the solvent was dichloromethane. In the more polar solvent, dimethylformamide, this value rose to 12%. Therefore racemization is in the same range as that observed for the racemization-resistant azide procedure. The coupling of Cbz-L-aspartyl(O-t-Bu)-L-phenylalanine with valine methyl ester is reported to be very sensitive to racemization.¹⁴ The tripeptide was prepared as described above, and the crude product was hydrolyzed. GLC showed the presence of 2-3% D-phenylalanine. Again, in contrast to the ynamine procedure,¹⁵ racemization seems to be no problem when push-pull acetylenes are used.

So far, the only observable disadvantage of the reagent is the somewhat long reaction time for the coupling of the activated amino acids (or peptides) with the amine component. The increase in reaction time t_2 could be a limiting factor, if longer peptide fragments are to be linked.

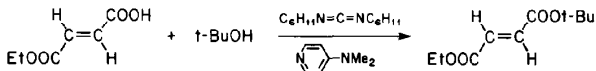
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 1-(4-Chlorophenyl)-3-(4'-methyl-1-piperaziny)-2-propyn-1-one: Piperazine, 1-
[3-(4-chlorophenyl)-1-oxo-2-propynyl]-4-methyl- (9); (42122-11-2)
- Benzylloxycarbonyl-L-alanyl-L-cysteine methyl ester: L-Cysteine, N-[N-
[(phenylmethoxy)carbonyl]-L-alanyl]-, methyl ester (9); (34804-98-3)
- Benzylloxycarbonyl-L-alanine: Alanine, N-carboxybenzyl ester, L- (8); L-
Alanine, N-[(phenylmethoxy)carbonyl]- (9); (1142-20-7)
- L-Cysteine methyl ester hydrochloride: Cysteine, methyl ester, hydrochloride,
L- (8); L-Cysteine, methyl ester, hydrochloride (9); (18598-63-5)
- N-Methylmorpholine: Morpholine, 4-methyl- (8, 9); (109-02-4)
- Benzylloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl
ester: L-Valine, N-[N-[N-[(phenylmethoxy)carbonyl]-L- α -aspartyl]-L-
phenylalanyl]-, 4-(1,1-dimethylethyl) 1-methyl ester (10); (57850-41-6)
- Benzylloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine: L-
Phenylalanine, N-[N-[(phenylmethoxy)carbonyl]-L- α -aspartyl]-, 4-(1,1-
dimethylethyl) ester (10); (32771-88-3)
- L-Valine methyl ester hydrochloride: Valine, methyl ester, hydrochloride, L-
(8); L-Valine, methyl ester, hydrochloride (9); (6306-52-1)

**ESTERIFICATION OF CARBOXYLIC ACIDS WITH DICYCLOHEXYL-
CARBODIIMIDE/4-DIMETHYLAMINOPYRIDINE: tert-BUTYL ETHYL FUMARATE**
((E)-2-Butenedioic acid, ethyl 1,1-dimethylethyl ester)



Submitted by B. Neises and Wolfgang Steglich.¹

Checked by Cheryl Stubbs and Robert V. Stevens.

1. Procedure

Caution! Dicyclohexylcarbodiimide is a potent allergen and should be handled with gloves.

A 500-mL, one-necked flask, equipped with a calcium chloride drying tube is charged with 28.83 g (0.20 mol) of monoethyl fumarate (Note 1), 200 mL of dry dichloromethane (Note 2), 44.47 g (0.60 mol) of tert-butyl alcohol (Note 3) and 2.00 g (0.16 mol) of 4-dimethylaminopyridine (Note 4). The solution is stirred and cooled in an ice bath to 0°C while 45.59 g (0.22 mol) of dicyclohexylcarbodiimide (Note 5) is added over a 5-min period. After a further 5 min at 0°C the ice bath is removed and the dark brown reaction mixture is stirred for 3 hr at room temperature. Dicyclohexylurea which has precipitated is removed by filtration through a fritted Buchner funnel (G3), and the filtrate is washed with two 50-mL portions of 0.5 N hydrochloric acid

(Note 6) and two 50-mL portions of saturated sodium bicarbonate solution. During this procedure some additional dicyclohexylurea is precipitated, which is removed by filtration of both layers to facilitate their separation. The organic solution is dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure, affording, after a small forerun, 30.5-32.5 (76-81%) of tert-butyl ethyl fumarate, bp 105-107°C (12 mm) (Note 7).

2. Notes

1. Monoethyl fumarate was purchased from Ega-Chemie, D-7924 Steinheim, Germany.
2. Dichloromethane was freshly distilled over P_4O_{10} .
3. tert-Butyl alcohol was purchased from E. Merck, D-6100 Darmstadt, Germany, and used without further purification.
4. 4-Dimethylaminopyridine was obtained from Schering AG, D-1000 Berlin, Germany. 4-Pyrrolidinopyridine, which is equally well suited as a catalyst in this reaction may be purchased from Ega-Chemie, D-7924 Steinheim, Germany.
5. Dicyclohexylcarbodiimide was freshly distilled with a Kugelrohr apparatus (Büchi GKR-50), bp 135-140°C (0.5 mm). It may be added either in crystalline form or dissolved in 50 mL of dry dichloromethane.
6. For esters more sensitive to acids, the use of concentrated aqueous citric acid solution is advisable.
7. The proton magnetic resonance spectrum of the product in chloroform-d shows the following absorptions: δ 1.30 (t, 3 H, $J = 7.5$, CH_3CH_2), 1.50 (s, 9 H, $C(CH_3)_3$), 4.23 (q, 2 H, $J = 7.5$, CH_3CH_2), 6.77 (s, 2 H, $CH=CH$). tert-Butyl ethyl fumarate may be easily converted into ethyl fumarate by alkaline hydrolysis.

3. Discussion

This procedure offers a convenient method for the esterification of carboxylic acids with alcohols^{2,3,4} and thiols² under mild conditions. Its success depends on the high efficiency of 4-dialkylaminopyridines as nucleophilic catalysts in group transfer reactions.⁵ The esterification proceeds without the need of a preformed, activated carboxylic acid derivative, at room temperature, under nonacidic, mildly basic conditions. In addition to dichloromethane other aprotic solvents of comparable polarity such as diethyl ether, tetrahydrofuran, and acetonitrile can be used. The reaction can be applied to a wide variety of acids and alcohols, including polyols,^{2,4,6} α -hydroxycarboxylic acid esters,⁷ and even very acid labile alcohols like vitamin A.⁸ It has also been used for the esterification of urethane-protected α -amino acids with polymeric supports carrying hydroxy groups.⁹ In this case, however, some racemization of the amino acid is observed, because of 2-alkoxyoxazolin-5-one formation.¹⁰ Racemization can be decreased by shortening the coupling time¹⁰ or completely avoided by working with N-(p-nitrophenylsulfonyl)amino acids.¹¹

With increasing steric hindrance, the rate of esterification is decreased and the formation of N-acylureas may become a serious side reaction. This is indicated by the decrease in yield in the esterification of 2,5-cyclohexadiene-1-carboxylic acid with different alcohols: MeOH (95%), EtOH (84%), i-PrOH (75%), n -C₆H₁₁OH (65%), t-BuOH (65%).¹² Diminished acidity because of the influence of electron-donating substituents in aromatic carboxylic acids can also lead to low yields.

The dicyclohexylcarbodiimide/4-dialkylaminopyridine method is also well suited to the synthesis of a wide variety of thiol esters.^{2,13}

4-Dimethylaminopyridine also catalyzes the formation of esters and thiol esters in the reaction of mixed carboxylic anhydrides¹⁴ or 2,4,6-trinitrophenyl esters¹⁵ with alcohols and thiols. 1-Acyl-4-benzylidene-1,4-dihydropyridines have been introduced recently as promising reagents for the synthesis of sterically hindered esters.¹⁶ The current methods available for ester and thiol ester formation have been reviewed recently by Haslam.¹⁷

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

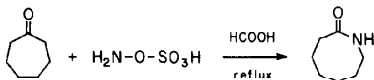
Dicyclohexylcarbodiimide: Carbodiimide, dicyclohexyl- (8); Cyclohexanamine, N,N'-methanetetraylbis- (9); (538-75-0)

4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

Monoethyl fumarate: Fumaric acid, monoethyl ester (8); 2-Butenedioic acid (E)-, monoethyl ester (9); (2459-05-4)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

HEXAHYDRO-2-(1H)-AZOCINONE
(2(1H)-Azocinone, hexahydro-)



Submitted by George A. Olah and Alexander P. Fung.¹

Checked by David Varie and Edwin Vedejs.

1. Procedure

A 100-mL, three-necked flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser connected to a nitrogen flow line. The system is dried with a heat gun while it is flushed with dry nitrogen. The reaction vessel is then cooled in a water bath while a light positive pressure of nitrogen is maintained. The flask is charged with hydroxylamine-O-sulfonic acid² (8.48 g, 0.075 mol) (Note 1) and 95-97% formic acid (45 mL) (Note 2). A solution of cycloheptanone (5.61 g, 0.05 mol) (Note 3) in 15 mL of 95-97% formic acid is added with stirring over a 3-min period. After addition is complete, the reaction mixture is heated under reflux for 3 hr and then cooled to room temperature. The reaction mixture is quenched with 75 mL of ice/water. The aqueous solution is slowly neutralized to pH ~ 7 with 6 N sodium hydroxide (Note 4) and extracted with three 100-mL portions of chloroform. The combined organic layers are dried with anhydrous

magnesium sulfate. After removal of the solvent on a rotary evaporator, the product hexahydroazocinone is purified by distillation to give 3.8-4.0 g (60-63%) bp 94-96°C/0.2 mm, (short path apparatus), lit⁴ bp 133-135°C/4 mm (Note 5).

2. Notes

1. The hydroxylamine-O-sulfonic acid used by the submitters was purchased from Ventron Corporation and used directly. However, it can be readily made in the laboratory.^{3,4}

2. Formic acid 95-97% was obtained from the Aldrich Chemical Company.

3. Commercial cycloheptanone (bp 179°C) obtained from MCB was used directly.

4. An external ice-salt bath is used.

5. The product exhibits the following spectra: ¹H NMR (CDCl₃) δ: 7.16 (br, 1 H, NH), 3.31 (m, 2 H, CH₂-N), 2.57 (m, 2 H, CH₂^{||}C), 2.40 (3 H, m), 1.6-1.8 (m, 6 H, CH₂); IR (cm⁻¹): 3270, 3200, 1650; GLC analysis: 20% SE 30, 60/80 on Chrom-W, 1/8" x 20' column, 180°C: one peak.

3. Discussion

The procedure described is a one-step conversion of cycloheptanone into hexahydro-2(1H)-azocinone. The method is general and is characterized by good yields, mild conditions, and easy preparation of the product in pure form from readily available starting materials. Several methods are described in the patent literature for simultaneous oximation of ketones and rearrangement to the corresponding oxime, including the use of hydroxylamine and sulfuric

acid^{6,7} or by employing primary nitroparaffins as a source of hydroxylamine.^{8,9} The present method has been shown¹⁰ to be applicable to a wide variety of lactams (C₅ ~ C₁₂). In the specific case of hexahydroazocinone, the yield from cycloheptanone (60-63%) appears lower than for the conventional two-step method,^{11,12} but the latter requires isolation of the intermediate oxime.

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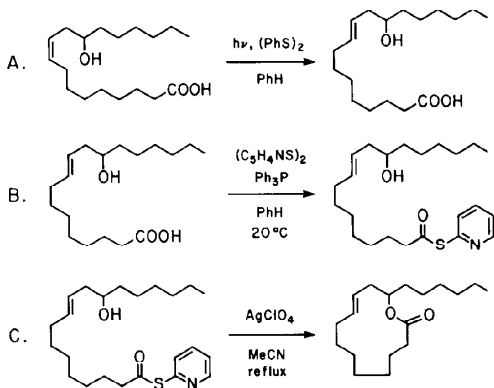
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Hexahydro-2(1H)-azocinone: 2(1H)-Azocinone, hexahydro- (9); (673-66-5)
Hydroxylamine-O-sulfonic acid (8,9); (2950-43-8)
Cycloheptanone (9); (502-42-1)
Formic acid (8,9); (64-18-6)

RICINOLEIC ACID LACTONE

(9-Octadecenoic acid, 12-hydroxy-, [(+)-(R)-trans]-, lactone)



Submitted by Adolf Thalmann, Konrad Oertle, and Hans Gerlach.¹

Checked by James R. Pribish and Edwin Vedejs.

1. Procedure

A. *Ricinolaidic acid*. Ricinolic acid (Note 1) (39.75 g, 0.106 mol) and 586 mg (2 mol %) of diphenyl disulfide dissolved in 1000 mL of hexane are placed in a photochemical reactor (Note 2) and irradiated for 3 hr with a Philips HP(L) 250-watt medium pressure mercury lamp. After irradiation the solvent is removed under reduced pressure and the semisolid residue is recrystallized from 185 mL of hexane to yield 11.3 g of crude ricinolaidic acid, mp 39–43°C. The irradiation is repeated with the mother liquor under

the same conditions to yield, after removal of the solvent and recrystallization of the residue from 135 mL of hexane, an additional 7.2 g, mp 38-42°C; total yield of crude ricinelaidic acid is 18.5 g (58%). The product after recrystallization from 220 mL of hexane weighs 15.6 g (49%), mp 43-45°C and is suitable for the following step. Repeated recrystallization from hexane yields ricinelaidic acid with mp 51.0-51.5°C (Notes 3 and 4).

B. *Ricinelaidic acid S-(2-pyridyl)carbothioate*. In a dry, stoppered 10-mL flask containing a magnetic stirring bar are placed 360 mg (1.2 mmol) of ricinelaidic acid (see above), 308 mg (1.4 mmol) of 2,2'-dipyridyl disulfide (Note 5), 1 mL of benzene and 367 mg (1.4 mmol) of triphenylphosphine, and the mixture is stirred for 30 min. The resulting slurry is then dissolved in 55 mL of dry acetonitrile (Note 6).

C. *Ricinelaidic acid lactone*. Dry acetonitrile (100 mL), 3.5 mL of 1 M silver perchlorate in toluene (Notes 7 and 8), and a magnetic stirring bar are placed in a 500-mL flask equipped with a reflux condenser that carries a Hershberg dropping funnel. The solution is heated in an oil bath so that the boiling acetonitrile returns from the condenser at the rate of 5 to 10 drops per sec (Note 9). Then the acetonitrile solution of the ricinelaidic acid S-(2-pyridyl)carbothioate is added dropwise during 1 hr through the condenser to the magnetically stirred refluxing silver perchlorate solution (Note 9). The slightly turbid mixture is boiled for an additional 15 min and the solvent is removed under reduced pressure in a rotatory evaporator. The residue is diluted with 30 mL of 0.5 M potassium cyanide solution and the mixture containing suspended solids is extracted with three 50-mL portions of benzene. The benzene extracts are washed with 30 mL of water, dried with anhydrous magnesium sulfate, and filtered, and the solvent is removed under reduced pressure. Crude product is obtained as an oil (710 mg). It can be

purified by chromatography on 40 g of silica gel (Note 10) with benzene as eluant. Fractions of 10 mL are collected at 30-min intervals. Fractions 7 to 19 contain 283 to 296 mg (84-88%) of ricinelaidic acid lactone (Note 11).

2. Notes

1. Technical grade (80%) ricinolic acid was obtained from Fluka A.G. Buchs, Switzerland or from Tridom Chemicals, Inc. Saponification of methyl ricinoate² also gives suitable material.

2. The photochemical reactor used is quite similar to the one described in *Org. Synth., Collect. Vol. 5* 1973, 298.

3. The purity of the products has been checked by capillary gas liquid chromatography of the corresponding methyl ester obtained with ethereal diazomethane solution (Carlo Erba Fractovap 20 meter glass capillary coated with UCON HB at 160°C). Ricinelaidic acid, mp 49-50°C, contains 4%, that with mp 51.0-51.5°C, less than 1% of ricinolic acid. Submitters obtained higher yields (58%, mp 49-50°C), perhaps due to better quality starting material.

4. (+)-(R)-Ricinelaidic acid, mp 51.0-51.5°C, has an optical rotation of $[\alpha]_D +6.6^\circ$ (C₂H₅OH, c 10).

5. 2,2'-Dipyridyl disulfide obtained from Fluka A.G., Buchs, Switzerland, was recrystallized from hexane (30 mL/g) to yield a suitable product, mp 58-59°C.

6. Commercially available acetonitrile is distilled over phosphorus pentoxide.

7. Silver perchlorate monohydrate (9 g) (obtained from Fluka A.G.) is suspended in 110 mL of toluene together with a Teflon-coated magnetic stirring bar. The solution is magnetically stirred and heated in an oil bath until 70 mL of toluene has distilled.

8. The silver perchlorate solution may be substituted by 8.5 mL of 0.4 M silver trifluoromethanesulfonate (Fluka) in toluene.

9. This reflux rate is crucial for predilution of the carbothioate in the condenser. Lower reflux rates require an accordingly slower addition of the S-(2-pyridyl)carbothioate during 2 to 4 hr.

10. Silica gel 60 MERCK in a 2.5-cm diameter column was used.

11. The product distills at 110°C (0.01 mm) in a Kugelrohr distillation apparatus and has an optical rotation of $[\alpha]_D^{25} +42^\circ$ (CHCl₃, d 1).

3. Discussion

The silver-ion promoted lactonization of hydroxy-S-(2-pyridyl)-carbothioates was introduced by the submitters³ as a mild method for the synthesis of naturally occurring macrolides as, for example, nonactin⁴ and ricifeiolide⁵ from the corresponding hydroxy acids. If the method of Mukaiyama et al.⁶ is used for the formation of the S-(2-pyridyl)carbothioate no protection of the hydroxyl group is needed in this step. The cited examples show that silver-ion promoted lactonization can be used to effect ring closure of base-sensitive and unsaturated acid-sensitive hydroxy acids in good yield.

Similar methods to effect lactonization have been proposed by Corey et al.⁷ and Masamune et al.⁸ The first consists of prolonged heating of hydroxy-S-(2-pyridyl)carbothioates in boiling xylene; the second is the mercury trifluoroacetate-promoted cyclization of a hydroxy-S-tert-butyl carbothioate.

Ricinelaiddic acid was selected for the submitted procedure because it has a moderately complex structure and can be prepared easily from commercially available technical grade ricinolic acid. This conversion represents an

example of the facile cis-trans interconversion of olefins⁹ caused by photochemically generated phenylthiyl radicals leading to the thermodynamic equilibrium.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Ricinelaidic acid: 9-Octadecenoic acid, 12-hydroxy-, [R-(E)]- (9); (540-12-5)

Ricinolic acid: 9-Octadecenoic acid, 12-hydroxy-, [R-(Z)]- (9); (141-22-0)

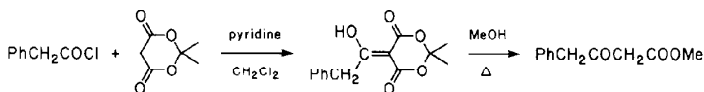
Diphenyl disulfide: Phenyl disulfide (8); Disulfide, diphenyl (9); (882-33-7)

2,2'-Dipyridyl disulfide: Pyridine, 2,2'-dithiodi- (8); Pyridine, 2,2'-dithiobis- (9); (2127-03-9)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Silver perchlorate: Perchloric acid, silver(1 +) salt, monohydrate (8,9); (14242-05-8)

**METHYL PHENYLACETYLACETATE FROM PHENYLACETYL
CHLORIDE AND MELDRUM'S ACID**
(Benzenebutanoic acid, β -oxo-, methyl ester)



Submitted by Y. Oikawa, T. Yoshioka, K. Sugano, and Osamu Yonemitsu.¹

Checked by Michael J. Taschner, Hans P. Märki, and Clayton H. Heathcock.

1. Procedure

Into a 300-mL, round-bottomed flask equipped with a dropping funnel and a magnetic stirrer is placed a solution of 23.75 g (0.165 mol) of recrystallized Meldrum's acid (Note 1) in 65 mL of anhydrous dichloromethane. The flask and its contents are cooled in an ice-bath, and 32.5 mL (0.40 mol) of anhydrous pyridine (Note 2) is added with stirring under an argon atmosphere over a period of 10 min. To the resulting colorless clear solution is added a solution of 25.0 g (0.16 mol) of freshly distilled phenylacetyl chloride (Note 3) in 50 mL of anhydrous dichloromethane over a period of 2 hr. After the addition is complete, the resulting orange, cloudy reaction mixture is stirred for 1 hr at 0°C , then for an additional 1 hr at room temperature. The reaction mixture is diluted with 35 mL of dichloromethane, and then poured into 100 mL of 2 N hydrochloric acid containing crushed ice. The organic phase is separated and the aqueous layer extracted twice with 25-mL portions

of dichloromethane. The organic phase and the extracts are combined, washed twice with 25-mL portions of 2 N hydrochloric acid and 30 mL of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator to yield an acyl Meldrum's acid (Note 4) as a pale yellow solid.

The solid acyl Meldrum's acid, without purification, is refluxed in 250 mL of anhydrous methanol for 2.5 hr. The solvent is removed with a rotary evaporator, and the residual oil is distilled under reduced pressure to give 25.2 g (82%) of methyl phenylacetylacetate as a colorless liquid, bp 126-128°C/(0.6 mm).

2. Notes

1. Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, is available from the Aldrich Chemical Company, Inc. It may also be prepared from malonic acid and acetone.² It is used in this preparation after recrystallization from acetone or from acetone-hexane. The checkers found that a final product of significantly lower purity is obtained if the Meldrum's acid is not recrystallized.

2. The checkers used pyridine that had been distilled from calcium hydride.

3. Phenylacetyl chloride is supplied by Wako Pure Industries, Ltd. (Japan) and the Aldrich Chemical Company, Inc. It is distilled before use, bp 95-96°C/(12 mm). The checkers found the distilled commercial material to be slightly pink. However, material of this quality gave a good yield of pure product.

4. The product, 2,2-dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione is isolated in its enol form in 97% yield. If desired, it may be further purified by recrystallization from ether-hexane to give pale yellow prisms, mp 96-97°C (dec). The checkers recrystallized the material from dichloromethane-hexane and obtained 65% yield of material, mp 94-96°C (dec) and 7%, mp 84-90°C. The ^1H NMR spectrum of this compound has absorptions at δ 1.65 (s, 6 H), 4.30 (s, 2 H), 7.20 (s, 5 H), and 15.0 (br s, 1 H).

3. Discussion

Because β -keto esters are among the most important intermediates in organic synthesis, many methods have been developed for their synthesis.³ However, it is still desirable to have a general and practical method for preparation of β -keto esters of the general type $\text{RCOCH}_2\text{CO}_2\text{R}'$, and thence by alkylation with alkyl halides compounds of the type $\text{RCOCHR}''\text{CO}_2\text{R}'$.⁴ The available synthetic methods can be classified broadly in three categories: those involving acetoacetic esters,⁵ those involving mixed malonic esters,⁶ and those involving malonic acid half esters.⁷ The procedure described herein⁸ may be classified as one of the malonic ester methods. The procedure consists of two simple steps and it utilizes readily-accessible starting materials. When the carboxylic acid chloride is not available, the carboxylic acid may be condensed with Meldrum's acid in the presence of a condensing agent such as ethyl phosphorocyanidate.⁹

Methanolysis or ethanolysis of an acyl Meldrum's acid is performed simply by refluxing in methanol or ethanol solution. The products are methyl or ethyl β -keto esters, and they can usually be purified by distillation. When a higher ester (such as benzyl, *t*-butyl, or trichloroethyl) is required, it is

easily prepared by refluxing the acyl Meldrum's acid in benzene containing about three equivalents of the appropriate alcohol.

Recently, Melillo et al., applied this Meldrum's acid method with some modifications to the synthesis of thienamycin. A carboxylic acid was treated with carbonyldiimidazole, followed by treatment with Meldrum's acid to give an acyl Meldrum's acid, which was converted to a β -keto p-nitrobenzyl ester by refluxing in acetonitrile containing p-nitrobenzyl alcohol.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl phenylacetylacetate: Benzenebutanoic acid, β -oxo-methyl ester (9);
(37779-49-0)

Phenylacetyl chloride: Acetyl chloride, phenyl- (8); Benzeneacetyl chloride
(9); (103-80-0)

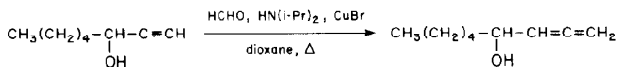
Meldrum's acid: Malonic acid, cyclic isopropylidene ester (8);

1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

ONE-STEP HOMOLOGATION OF ACETYLENES TO ALLENES:

PREPARATION OF 4-HYDROXYNONA-1,2-DIENE

(1,2-Nonadien-4-ol)



Submitted by Pierre Crabbé, Bahman Nassim and Maria-Teresa Robert-Lopes.¹

Checked by Jeffrey S. Stults and Edwin Vedejs.

1. Procedure

In a 500-mL, three necked flask, equipped with a thermometer, stirrer, and a reflux condenser with drying tube, are placed 12.6 g (0.1 mol) of 1-octyn-3-ol, 154 mL of dioxane, 7.24 g (0.0504 mol) of cuprous bromide, 7.4 g of paraformaldehyde and 18.54 g (0.183 mol) of diisopropylamine (Note 1). The resulting mixture is gently refluxed and stirred for 2 hr, and then cooled to room temperature and filtered through a Celite plug. The dark brown filtrate is concentrated under vacuum (Rotavapor) to a gummy residue and then diluted with 50 mL of water followed by 100 mL of ether and acidified with 6 N hydrochloric acid to pH 2. The ether-water layers are decanted from any residue, the ether layer is separated, and the aqueous solution is extracted with ether (5 x 50 mL). The ether extracts are combined and washed with small portions of water until pH 6.5 is reached. The organic layer is then washed with saturated sodium chloride solution and dried over anhydrous MgSO_4 . After

removal of ether by distillation through a 20-cm Vigreux column (water aspirator vacuum) while heating on a waterbath, $\leq 40^{\circ}\text{C}$, the residual liquid is fractionated under reduced pressure through a 10 cm Vigreux column. The main fraction is collected at $41\text{--}42.5^{\circ}\text{C}$ (0.15 mm) to give 8.65 g of pure allene (Note 2), with additional fractions of a less pure material.

2. Notes

1. Cuprous bromide and 1-octyn-3-ol were used as supplied by the Aldrich Chemical Company, Inc. Dioxane was dried over sodium/benzophenone and distilled, and diisopropylamine was distilled from barium oxide.

2. The spectral properties of 4-hydroxynona-1,2-diene are as follows: IR (neat) cm^{-1} : 3500 (OH), 1960 ($\text{C}=\text{C}=\text{C}$), 850 ($=\text{CH}$), 2900-2850 (CH). ^1H NMR (CDCl_3) δ : 0.65-1.7 (m); 4.15 (1 H, m); 4.8 (2 H, d of d, $J = 2.6$ Hz); 5.22, (1 H, q, $J = 6$ Hz).

3. Discussion

Although allenes were characterized long ago as a distinct class of organic substances, it is only recently that they have received proper attention from chemists, in particular for their potential in organic synthesis.² A number of methods are known for the transformation of acetylenes into allenes,³ but few are known which allow the homologation of an acetylenic group into a propadiene functionality.

A general procedure for the homologation of acetylenic compounds into allenes is described. The reaction conditions are mild and appear to be general, so that they can be applied to plain acetylenic substances as well as

to acetylenic alcohols, ethers, and esters. This procedure is essentially a one-step reaction. As such, it is simpler and faster than the previously reported technique which involves the conversion of an acetylenic compound into the Mannich base, the formation of its quaternary ammonium salt and the reduction of this salt with lithium aluminum hydride.⁴ Of great advantage over previously available methodology are the mild conditions, as well as the clean and fast procedure, which make this a method of choice for an efficient conversion of acetylenes to allenes.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

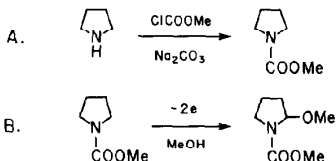
4-Hydroxynona-1,2-diene: 1,2-Nonadien-4-ol (10); (73229-28-4)

1-Octyn-3-ol (9); (818-72-4)

ANODIC OXIDATION OF N-CARBOMETHOXYPYRROLIDINE:

2-METHOXY-N-CARBOMETHOXYPYRROLIDINE

(1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester)



Submitted by T. Shono, Y. Matsumura, and K. Tsubata.¹

Checked by B. Schaer, G. Reymond, V. Toome, and Gabriel Saucy.

1. Procedure

A. N-Carbomethoxypyrrolidine. A 1-L, three-necked, round-bottomed flask is equipped with a 200-mL pressure-equalizing dropping funnel, a Graham condenser protected by a calcium chloride tube, and a mechanical stirrer. The flask is charged with 200 g (1.89 mol) of sodium carbonate (Note 1), 400 mL of methylene chloride (Note 2), and 71 g (1 mol) of pyrrolidine (Note 3). The dropping funnel is charged with 103 g (1.1 mol) of methyl chlorocarbonate (Note 3) which is added with stirring over a 2-hr period at a rate which sustains a gentle reflux. After the addition of methyl chlorocarbonate is completed, the reaction mixture is stirred overnight at room temperature. The

white precipitate is filtered with suction through a coarse Buchner funnel and washed three times with 100 mL of methylene chloride. The filtrate is concentrated on a vacuum rotary evaporator at a bath temperature of 30°C. The crude oily product is distilled under reduced pressure through a Claisen flask to yield 119-121 g (92-94%) of N-carbomethoxypyrrolidine, bp 64°C/1.3 mm.

B. *2-Methoxy-N-carbomethoxypyrrolidine*. A solution of N-carbomethoxypyrrolidine (12.7 g, 0.098 mol) and tetraethylammonium p-toluenesulfonate (0.83 g, 0.0027 mol) (Note 3) in 83 mL of methanol (Note 2) is added into an undivided jacketed cell (Note 4) equipped with two graphite-rod anodes and two graphite-rod cathodes, (Note 5) a thermometer, an exit tube for venting purposes, and a magnetic stirring bar. The carbon rods (0.6 cm in diameter, immersed 5.5 cm into the solution, resulting in a working electrode surface of 21.3 cm² and a current density of 46.9 mA/cm²) are spaced 4.5 mm apart. The anode rods and the two cathode rods are connected with #22 copper wire as shown in Figure 1. During the electrolysis (Note 6), the temperature of the reaction mixture is maintained at 10-15°C (Note 7) by cooling with tap water. After 2.34 F/mole of electricity (1A, 6 hr; the voltage between the anode and cathode was 19-24 V for the example in Figure 1) has been passed through, (Note 8) the current is stopped and the solvent is removed under reduced pressure. The residue is dissolved in 120 mL of methylene chloride and washed with aqueous NaCl (20 mL). The aqueous NaCl wash is re-extracted with methylene chloride (2 x 30 mL). The methylene chloride phases are combined and dried over magnesium sulfate. The solvent is evaporated and the residue is distilled, employing a Vigreux column, 5 cm, and an oil bath at 80-90°C (Note 9). The yield is 12.3-13.0 g (78-83%), bp 48-55°C/0.2-0.5 mm (Note 10).

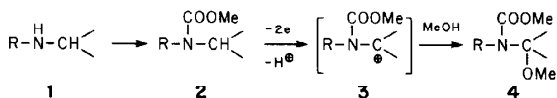
2. Notes

1. Sodium carbonate, anhydrous powder, supplied by J. T. Baker Chemical Company, is used directly.
2. Methylene chloride was purchased from Fisher Scientific Co.
3. Pyrrolidine was purchased from the Aldrich Chemical Company, and used without further purification.
4. The cell is shown in Figure 1.
5. The electrodes were purchased from Princeton Applied Research (PAR); Spectroscopic grade, Lot #174/78. This grade is not necessarily the best type of graphite for electrochemical purposes, but it was the only one immediately available. The submitters used graphite plates, purchased from Tokai Carbon Company, Inc., as electrodes, but they note that these are not the only electrode material usable in this reaction.
6. Princeton Applied Research (PAR) Potentiostat-Galvanostat, Model 173/179 was used.
7. According to the submitters the temperature should be kept below 50°C; otherwise lower yields are observed.
8. According to the submitters, if more than 2.2-2.5 F/mole of electricity is passed N-carbomethoxy-2,5-dimethoxypyrrolidine forms. The by-product can be separated by distillation (bp 64-65°C/1.0 mm).
9. An oil bath temperature higher than 100°C results in the formation of unsaturated carbamate formed by the elimination of methanol from the methoxylated carbamate. Accordingly, in the anodic methoxylation of carbamates having high boiling points, the product must be purified by column chromatography in order to avoid formation of the unsaturated carbamates.

10. The product has the following spectral properties: IR (liquid film) cm^{-1} : 2940, 2880, 1685, 1440, 1370, 1185, 1080, 950, 825, 770; ^1H NMR (CCl_4) δ : 1.48-2.21 (m, 4 H, CH_2 at C_3 and C_4 of pyrrolidine ring), 3.25 (s, 3 H, methoxy CH_3), 3.08-3.52 (m, 2 H, CH_2 at C_5 of pyrrolidine ring), 3.64 (s, 3 H, ester CH_3), 5.06 (m, 1 H, CH at C_2 of pyrrolidine ring).

3. Discussion

This procedure describes anodic α -methoxylation of carbamates (2) which are derived from primary and secondary amines (1).^{2,3}



The intermediate cations (3) are trapped with methanol to yield α -methoxycarbamates, 4, which are sufficiently stable to be stored for a long period. Table I shows other examples of anodic synthesis of 4.

The high regioselectivity in the methoxylation of unsymmetrical carbamates is remarkable (see 2-pipecoline carbamate and N-carbomethoxyproline methyl ester in Table I). The methoxylation always takes place in the order of $\text{CH}_3- > >\text{CH}_2 > -\text{CH}$.

α -Methoxycarbamates (4) are useful intermediates in organic syntheses, since treatment of 4 with Lewis acids or Brønsted acids regenerates 3 which can be trapped with a variety of nucleophiles. Thus, physiologically active compounds such as alkaloids,³ amino acids,⁴ nitrogen-containing phosphorus compounds,⁵ and pyridoxine⁶ can be synthesized using 4 as key starting compounds. Figure 2 summarizes the transformations.^{3,7}

Figure 1
Electrolysis Cell for Methoxylation

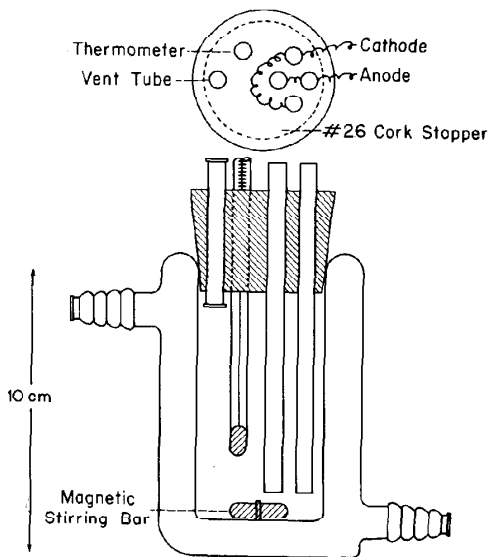


Figure 2

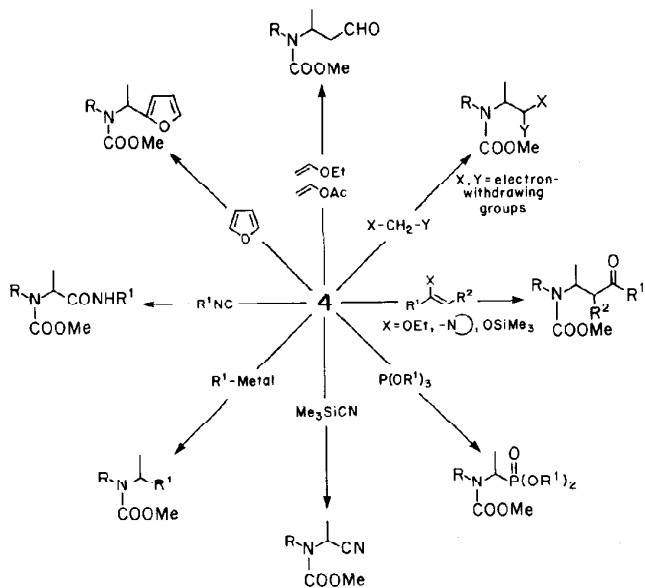



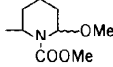
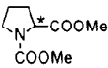
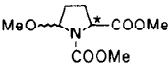

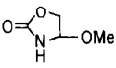

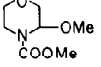

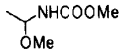
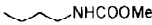
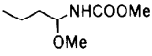

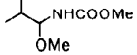
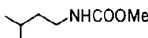
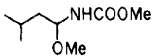


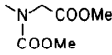
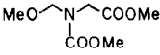


TABLE I
ANODIC SYNTHESIS OF α -METHOXYCARBAMATES

Carbamate	Electricity Passed F/mole	α -Methoxycarbamate	% Yield
	2.7		86
	2.6		69
	2.5		87
	3.0		89
	2.7		55
	4.85		83
	10.2		88
	6.0		70
	7.1		77
	2.1		72
	3.2		94

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

N-Carbomethoxypyrrolidine: 1-Pyrrolidinecarboxylic acid, methyl ester (9); (56475-80-0)

2-Methoxy-N-carbomethoxypyrrolidine: 1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester (9); (56475-88-8)

Pyrrolidine (8,9); (123-75-1)

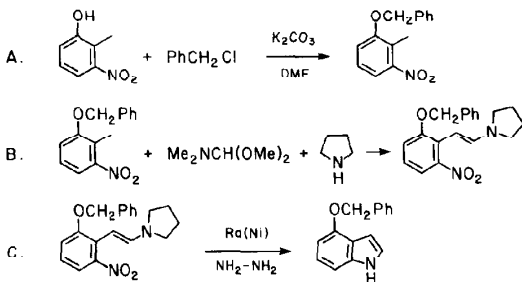
Methyl chlorocarbonate: Formic acid, chloro-, methyl ester (8);

Carbonochloridic acid, methyl ester (9); (79-22-1)

Tetraethylammonium p-toluenesulfonate: Ammonium, tetraethyl-, p-toluenesulfonate (8); Ethanaminium, N,N,N-triethyl-, salt with

4-methylbenzenesulfonic acid (1:1) (9); (733-44-8)

**INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH
FORMAMIDE ACETALS FOLLOWED BY REDUCTION: 4-BENZYLOXYINDOLE**
(1 H-Indole, 4-(phenylmethoxy)-)



Submitted by Andrew D. Batcho¹ and Willy Leimgruber.²

Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. *6-Benzyloxy-2-nitrotoluene*. A stirred mixture of 124.7 g (0.81 mol) of 2-methyl-3-nitrophenol (Note 1), 113.2 g (0.90 mol) of benzyl chloride, 112.2 g (0.81 mol) of anhydrous potassium carbonate, and 800 mL of dimethylformamide (DMF) is heated at 90°C for 3 hr. Most of the DMF is removed on a rotary evaporator (20 mm) and the oily residue is poured into 400 mL of 1 N sodium hydroxide and extracted with ether (3 x 800 mL). The combined extracts are dried (Na₂SO₄), filtered, and evaporated to give 203.5 g

of yellowish solid. Recrystallization from 1 L of methanol cooled to 0°C affords 177.6 (90%) of 6-benzyloxy-2-nitrotoluene as pale yellow crystals, mp 61-63°C³ (Note 2).

B. *(E)*-6-Benzyloxy-2-nitro- β -pyrrolidinostyrene. To a solution of 175.4 g (0.72 mol) of 6-benzyloxy-2-nitrotoluene in 400 mL of DMF are added 102.5 g (0.84 mol) of *N,N* dimethylformamide dimethyl acetal (Note 3) and 50.8 g (0.84 mol) of pyrrolidine. The solution is heated at reflux (110°C) for 3 hr (Note 4) under nitrogen and allowed to cool to room temperature. The volatile components are removed on a rotary evaporator, and the red residue (Note 5) is dissolved in 200 mL of methylene chloride and 1.60 L of methanol. The solution is concentrated to a volume of about 1.40 L on the steam bath and then is cooled to 5°C. Filtration and washing of the filter cake with 200 mL of cold methanol affords 209.8 g of red crystals, mp 87-89°C (Note 6). The mother liquors are evaporated, and the residue is recrystallized from 50 mL of methanol (5°C) to give an additional 12.30 g of red solid, mp 81-83°C (Note 7). Thus the total yield is 222.1 g (95%) of a 15:1 mixture of *(E)*-6-benzyloxy-2-nitro- β -pyrrolidinostyrene (Note 8) and *(E)*-6-benzyloxy- β -dimethylamino-2-nitrostyrene.

C. 4-Benzyloxyindole. To a stirred solution of 162.2 g (0.50 mol) of *(E)*-6-benzyloxy-2-nitro- β -pyrrolidinostyrene (Note 9) in 1 L of THF and 1 L of methanol at 30°C under nitrogen is added 10 mL of Raney nickel (Note 10) followed by 44 mL (0.75 mol) of 85% hydrazine hydrate. Vigorous gas evolution is observed. The red color turns to dark brown within 10 min and the reaction temperature rises to 46°C. An additional 44 mL of 85% hydrazine hydrate is added after 30 min and again 1 hr later. The temperature is maintained between 45-50°C with a water bath during the reaction and for 2 hr after the last addition. The mixture is cooled to room temperature and the catalyst is

removed by filtration through a bed of Celite (Note 11) and is washed several times with methylene chloride. The filtrate is evaporated and the residue dried by evaporating with 500 mL of toluene. The reddish residue (118.5 g), dissolved in ca. 1 L of toluene-cyclohexane (1:1), is applied to a column of 500 g of silica gel (70-230 mesh, Merck) prepared in the same solvent. Elution with 6.0 L of toluene-cyclohexane (1:1) followed by 3 L of toluene-cyclohexane (1:2) affords 108.3 g of white solid which is crystallized from 150 mL of toluene and 480 mL of cyclohexane (Note 12). A total of 107.3 g (96% yield) of 4-benzyloxyindole (Note 13) is obtained in three crops as white prisms, mp 60-62°C (Note 14).

2. Notes

1. 2-Methyl-3-nitrophenol was obtained from Aldrich Chemical Company, Inc.

2. The ^1H NMR spectrum is as follows δ : 7.35 (m, 5 H), 7.13 (m, 3 H), 5.10 (s, 2 H), 2.42 (s, 3 H).

3. N,N-Dimethylformamide dimethyl acetal was prepared according to a procedure of Bredereck.⁴ N,N-Dimethylformamide diethyl acetal can also be used. Both the dimethyl and the diethyl acetal are commercially available from Aldrich Chemical Company, Inc.

4. The reaction was followed by TLC on silica gel plates developed with ether-pet. ether (1:1).

5. Since it contained non-volatile N-formylpyrrolidine, direct reduction of the crude material was not attempted.

6. This crop contained 5% 6-benzyloxy- β -dimethylamino-2-nitrostyrene (by NMR). Pure 6-benzyloxy-2-nitro- β -pyrrolidinostyrene melts at 91.5-92.5°C.

7. This crop contained 15% 6-benzyloxy- β -dimethylamino-2-nitrostyrene (by NMR).

8. The ^1H NMR spectrum is as follows δ : 7.75 (d, 1 H, $J = 12.2$), 7.25 (m, 6 H), 6.91 (dd, 2 H, $J = 9$), 5.20 (d, 1 H, $J = 12.2$), 5.03 (s, 2 H), 3.08 (m, 4 H), 1.8 (m, 4 H).

9. This compound may contain varying amounts of 6-benzyloxy- β -dimethylamino-2-nitrostyrene.

10. Raney nickel is commercially available as type #28 from the Davison Chemical Division of W. R. Grace and Co.

11. The catalyst is pyrophoric and should not be sucked dry.

12. The material tenaciously holds hydrocarbons, such as pentane, hexane, and petroleum ether, which cannot be removed even under high vacuum. The solvated crystals show hydrocarbon protons in the NMR and exhibit a broad melting point. However, we have found that cyclohexane is not retained in the crystals.

13. The ^1H NMR spectrum is as follows δ : 7.9 (br s, 1 H), 7.32 (m, 5 H), 6.95 (m, 3 H), 6.65 (m, 2 H).

14. We could not reproduce the reported⁵ mp 72-74°C (toluene). The material has the proper microanalysis and is pure by NMR and TLC.

3. Discussion

Through the years, widespread interest in the synthesis of natural products and their analogs bearing the oxygenated indole nucleus has led to the development of several routes to protected hydroxylated indoles. However, 4-benzyloxyindole was first prepared relatively recently in modest overall yield by the Reissert method, which involves condensation of 6-benzyloxy-2-

nitrotoluene with ethyl oxalate, reductive cyclization to the indole-2-carboxylate, hydrolysis to the acid, and decarboxylation.⁵

Although a variety of synthetic methods have been used to prepare indoles^{6,7} many of these lack generality and are somewhat restrictive since they employ conditions, e.g., acid or strongly basic cyclizations or thermal decarboxylations, which are too harsh for labile substituents. This efficient, two-step procedure^{8,9} illustrates a general, simple, and convenient process for preparing a variety of indoles substituted in the carbocyclic ring, as can be seen in Table I. Since many of these examples served to determine the scope of this method, the yields in most cases have not been optimized. In many cases, the starting materials are readily available or can be easily prepared.

As can be seen in Table I, variation of the substituent has a profound effect on the rate of reaction of the o-nitrotoluene derivative with dimethylformamide acetals, but has little effect on the yields, which are often almost quantitative. As can be predicted, electron withdrawing groups accelerate the reaction. To shorten the somewhat lengthy reaction times which are often necessary when electron-donating substituents are present, more reactive aminomethylenating reagents such as pyrrolidine (or piperidine) acetals,⁸ aminals,¹⁰ or trisaminomethanes¹¹ can be employed. Alternatively, as described above, simply adding pyrrolidine to the reaction mixture also generates in situ a very effective aminomethylenating reagent.^{12,13} Thus, for example, in the case of 6-benzyloxy-2-nitrotoluene, the reaction with N,N-dimethylformamide dimethyl acetal requires 51 hr versus 3 hr when pyrrolidine is added. Pyrrolidine undergoes exchange reactions with N,N-dimethylformamide acetals to produce an equilibrium mixture of formylpyrrolidine acetal and the mixed pyrrolidine dimethylamine aminal (alkoxydimethylaminopyrrolidinomethane)

as well as other trisaminomethane species.¹⁴ (In cases where pyrrolidine reacts with the aromatic substrate, addition of the substrate can be delayed until pyrrolidine exchange is complete.) This mixture of reagents gives rise to condensation products - pyrrolidine enamines which contain 5-10% of the corresponding N,N-dimethylenamines.

The enamine intermediates are usually crystalline, red compounds which can be stored at room temperature for reasonable periods. In cases where the enamines are non-crystalline, it is recommended that the crude product be used directly in the next step, since purification is, in such cases, not practical. Although the more volatile derivatives can be distilled under high vacuum, this entails some risk because of their thermal instability. Moreover, the enamines are not stable to silica gel (TLC or column) chromatography.

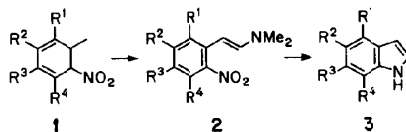
Conversion of the intermediate nitroenamine into the indole requires selective reduction of the nitro group. Catalytic hydrogenation results in spontaneous formation of the indole and is generally the mildest and most convenient method of reduction. Although selectivity does vary with the substituent on the aromatic ring, it is generally highly in favor of the nitro group. However, scale-up requires access to large autoclaves or special equipment. To avoid hydrogenolysis of benzyl or chloro functions, Raney nickel is the catalyst of choice. Excellent yields have been obtained using hydrazine and the appropriate catalyst¹⁵ as, in essence, a hydrogenation process which does not require an autoclave or special equipment and can be easily carried out in the laboratory.

Alternative methods of reduction have also been used: sodium dithionite,¹⁶ iron in acetic acid,¹⁷ stannous chloride,¹⁷ and titanium trichloride.¹⁸

This method has been applied to the preparation of polycyclic indoles^{12,19} and azaindoles^{19,20,21} as well.

TABLE I

INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH N,N-DIMETHYLFORMAMIDE ACETALS AND REDUCTION



Substituents				Interme- diates 2	Reaction Time	Purified Yield % (Procedure) ^a	Indoles 3	Yield % (Procedure) ^b	References
R ₁	R ₂	R ₃	R ₄	mp or bp/mm			mp or bp/mm		
-----	---	---	---	125°/0.03	22 hr	97(M,E)	52.5 - 53.5°	80(A)	8,9
OCH ₂ Ph	---	---	---	67 - 68°	51 hr	90(M)	60 - 62°	70(B)	12
----	OCH ₂ Ph	---	---	98 - 99°	29 hr	78(E)	103 - 105°	45(B) [64] ^c	8,9,12
----	---	OCH ₂ Ph	---	108.5-110°	41 hr	97(M)	118 - 120°	75(B) ⁱ	12
----	OCH ₂ Ph	OCH ₂ Ph	---	99.5-101°	48 hr	86(M)	112 - 113°	54(B) ^j	8,9
----	OCH ₂ Ph	CH ₃	---	113 - 134°	31 hr	87(M)	82 - 83°	84(B)	12
----	OCH ₃	---	---	68.5-70°	16 hr	92(M)	56.5 - 57.5°	83(A)	8,9
----	---	OCH ₃	---	152°/0.06	70 hr	64(E)	88 - 90°	63(A) [62] ^f	8,9,12

----	OCH ₃	OCH ₃	---	125 - 126°	48 hr	68(M)	154 - 155°	28(A)	8,9
----	OCH ₃	---	CH ₃	100 - 101°	8 hr	54(M)	100 - 110°/0.15	66(A)	22
----	OCH ₂ O	---	---	114 - 116°	18 hr	72(E)	110 - 111°	50(A) [52] ^C	8,9,12
Cl	---	---	---	111°/0.03	6 hr	89(E)	90°/0.04	63(B)	8,9
----	Cl	---	---	81.5-82.5°	7 hr	88(E)	71 - 72°	78(B)	8,9
----	---	Cl	---	44 - 46°	24 hr	57(M)	86.5 - 88°	52(B) [75] ^C	8,9,12
----	---	NH ₂ ^d	---	173 - 174°	2 hr	82(E) ^f	77.5 - 78.5°	43(A)	8,9,12
CN	---	---	---	66 - 68°	3 hr	93(M)	116 - 117°	67(C)	17
----	---	CN	---	134 - 137.5°	2.5 hr	86(E)	128 - 129°	65(A)	8,9
----	F	---	---	57.5 - 59°	3.5 hr	92(E)	46.5 - 47°	51(B)	8,9
----	---	F	---	46 - 47°	22 hr	63(M)	74 - 75°	80(B) [80] ^C	8,12
CH ₃	---	---	---	108°/0.05	24 hr	70(E)	82°/0.4	57(A)	8,9
----	---	CH ₃	---	41.5 - 43.5°	37 hr	83(M)	29 - 30.5°	83(A)	23
----	---	---	CH ₃	76 - 76.5°	46 hr	40(E)	83 - 84°	48(A)	8,9
----	---	CH(CH ₃) ₂	---	138-140°/0.06	42 hr	84(E)	40 - 41°	51(A)	8,9
----	---	CH(OCH ₃) ₂	---	67 - 68°	8 hr	55(E)	62 - 63.5°	31(A)	8,9
COOCH ₃	---	---	---	120-130°/0.2	6 hr	86(M)	63°	82(A) [63] ^C	17,24
COOC ₂ H ₅	---	---	---	(oil)	5 days	93(E)	67 - 69°	38(D)	17

----	COOC ₂ H ₅ ^e	---	---	55 - 56.5°	4.5 hr	70(E)	95 - 96°	39(A)	8,9
----	----	----	COOCH ₃	132 - 134°	9 hr	88(M)	46 - 48°	72(A) ^g	12
Cl	OCH ₃	---	---	----	overnight	--(M)	109 - 111°	(B) [59] ^c	25
----	OCH ₃	Cl	---	140 - 141°	overnight	78(M)	126 - 128°	46(B) [45] ^c	25
----	OCH ₃	F	---	116 - 117°	overnight	64(M)	73 - 74°	54(B)	25
----	----	Br	---	----	31 hr	--(M)	93°	37(B) ^h	26

^a(M) = N,N-Dimethylformamide dimethyl acetal; (E) = N,N-dimethylformamide diethyl acetal.

^bA = catalytic hydrogenation in benzene using palladium on charcoal; B = catalytic hydrogenation in benzene using Rarey nickel; C = iron in acetic acid; D = stannous chloride.

^cYield in brackets represents overall yield without purification of intermediate 2.

^dR₃ = NO₂ in compounds 1 and 2.

^eR₂ = COOH in compound 1.

^fNo solvent was used.

^gMethanol was the solvent.

^hEthanol was the solvent.

ⁱ(M) + pyrrolidine gave a mixture (10:1) of pyrrolidine enamine, mp 108-110° (MeOH), and N,N-dimethylenamine (5 hr reflux, 97% yield) which, on reduction (Raney nickel-hydrazine), gave the indole (93% yield).

^j(M) + pyrrolidine gave a mixture (9:1) of pyrrolidine enamine and N,N-dimethylenamine (5 hr reflux, 95% yield) which, on reduction (Raney nickel-hydrazine), gave the indole (89% yield).

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Benzoyloxyindole: Indole, 4-benzyloxy- (8); 1 H-Indole, 4-(phenylmethoxy)- (9); (20289-26-3)

6-Benzoyloxy-2-nitrotoluene: Benzene, 2-methyl-1-nitro-3-(phenylmethoxy)- (9); (20876-37-3)

2-Methyl-3-nitrophenol: o-Cresol, 3-nitro- (8); Phenol, 2-methyl-3-nitro- (9); (5460-31-1)

Benzyl chloride: Toluene, α -chloro- (8); Benzene, (chloromethyl)- (9); (100-44-7)

N,N-Dimethylformamide dimethyl acetal: Trimethylamine, 1,1-dimethoxy- (8); Methanamine, 1,1-dimethoxy-N,N-dimethyl- (9), (4637-24-5)

Pyrrolidine (8,9); (123-75-1)

(E)-6-Benzoyloxy- β -dimethylamino-2-nitrostyrene: Ethenamine, N,N-dimethyl-2-[2-nitro-6-(phenylmethoxy)phenyl]-, (E)- (10); (78283-20-1)

WARNING

It has been reported^{1,2} that serious explosions have occurred during the preparation of tetramethylbiphosphine disulfide by the method described in *Inorganic Syntheses*.³ No such incidents have been reported in the synthesis of the compound published in this series,⁴ but the two procedures are sufficiently similar that caution is indicated. The following precautions are strongly urged:

- (1) The phosphorus trichloride sulfide (PSCl_3) should be distilled before use.
- (2) The reaction vessel should be cooled with an ice-salt bath (rather than an acetone-dry ice bath as specified in the published procedure) during the addition of the PSCl_3 solution to the Grignard reagent. The reaction temperature should be monitored carefully. If it falls below -5° , the addition should be stopped and the reaction mixture cautiously rewarmed to $0-5^\circ$ before addition is resumed.
- (3) The reaction apparatus should be shielded throughout the addition of the PSCl_3 solution and the subsequent warming of the reaction mixture.

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Unchecked Procedures

Accepted for checking during the period September 1, 1983 through September 1, 1984. An asterisk (*) indicates that the procedure has been subsequently checked.

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- 2292* Di-tert-Dutyl Methylenemalonate
P. Ballsteros and B. W. Roberts, Department of Chemistry,
University of Pennsylvania, Philadelphia, PA 19104
- 2293* 1,3-Dimethyl-3-methoxy-4-phenylazetidinone
L. S. Hegedus, M. A. McGuire, and L. M. Schultze, Department of
Chemistry, Colorado State University, Fort Collins, CO 80523
- 2294R* 1,3-Dimethylimidazole-2-thione
B. L. Benac, E. M. Burgess and A. J. Arduengo, III, School of
Chemical Sciences, 270 Roger Adams Laboratory, Box 57, 1209 W.
California Street, Urbana, IL 61801
- 2296 Ring Expansion and Cleavage of Succinoin Derivatives:
Spiro[4.5]decane-1,4-dione and Ethyl 4-Cyclohexyl-4-oxobutanoate
E. Nakamura and I. Kuwajima, Department of Chemistry, Tokyo
Institute of Technology, Meguro, Tokyo 152, Japan
- 2297 Trimethylsilylacetylene
A. B. Holmes and C. N. Sporikou, University Chemical Laboratory,
Lensfield Road, Cambridge, CB2 1EW, United Kingdom
- 2298 1,4-Bis(Trimethylsilyl)buta-1,3-diyne
G. E. Jones, D. A. Kendrick and A. B. Holmes, University Chemical
Laboratory, Lensfield Road, Cambridge, CB2 1EW, United Kingdom
- 2300 Ambient Temperature Ullmann Reaction: 4,5,4',5'-Tetramethoxy-1,1'-
biphenyl-2,2'-dicarboxaldehyde
F. E. Ziegler, K. W. Fowler, W. B. Rodgers, and R. T. Wester,
Department of Chemistry, Yale University, New Haven, CT 06511
- 2302* 2-Pentyl-3-methyl-cyclopent-2-en-1-one (DIHYDROJASMONE)
H. Stetter, H. Kuhlmann and W. Haese, Institut für Organische Chemie
der Rheinisch-Westfälischen Technischen Hochschule Aachen, West
Germany
- 2303* α -Hydroxylation of a Ketone Using o-Iodosylbenzoic Acid: α -
Hydroxyacetophenone via the α -Hydroxydimethylacetal
R. M. Moriarty, K.-C. Hou and S. K. Arora, Department of Chemistry,
University of Illinois at Chicago, Chicago, IL 60680
- 2304 (R)-(+)- and (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
(BINAP)
H. Takaya and R. Noyori, Department of Chemistry, Faculty of
Science, Nagoya University, Chikusa-ku, Nagoya 464, Japan
- 2305R* 6-Bromo-6-deoxy Hexose Derivatives by Ring-Opening of Benzylidene
Acetals with N-Dromosuccinimide
S. Hanessian, Department of Chemistry, University of Montreal, C.P.
6210, Succursale A., Montreal (Que.), Canada H3C 3V1
- 2306* 4-Nitroindole
J. Bergman and P. Sand, Department of Chemistry, Royal Institute of
Technology, S-100 44, Stockholm, Sweden

- 2307 (R)-(+)-Citronellal via Asymmetric Isomerization of N,N-Diethylnerylamine or N,N-Diethylgeranylamine
K. Tani, T. Yamagata and S. Otsuka, Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, 560, Japan
- 2308 Telomerization of Isoprene with Dialkylamine: N,N-Diethylnerylamine
K. Takabe, T. Yamada, T. Katagiri, and J. Tanaka, Department of Synthetic Chemistry, Faculty of Engineering, Shizuoka University, Johoku, Hamamatsu 432, Japan
- 2309 Addition of Dialkylamine to Myrcene: N,N-Diethylgeranylamine
K. Takabe, T. Katagiri, J. Tanaka, T. Fujita, S. Watanabe, and K. Suga, Department of Synthetic Chemistry, Faculty of Engineering, Shizuoka University, Johoku, Hamamatsu 432, Japan
- 2310 (-)- α -Pinene by Isomerization of (-)- β -Pinene
C. A. Brown and P. K. Jadhav, Chemical Dynamics Department, IBM, 5600 Cottle Road, San Jose, CA 95193
- 2311 Chiral 1,3-Oxathiane from (+)-Pulegone [Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin]
E. L. Eliel, J. E. Lynch, F. Kume, and S. V. Frye, Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27514
- 2315 Alkoxyacylation of Propargyl Chloride: Methyl 4-Chloro-2-butyrate
M. Olomucki and J. Y. Le Gall, Biochimie Cellulaire, College de France, 11, Place Marcellin-Berthelot, 75231 Paris Cedex 05, France
- 2316 Dibenzothiophene-4-thiol
K. Y. Jen and M. P. Cava, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104
- 2318 Synthesis of Macrocyclic Sulfides Using Cesium Thiolates
J. Buter and R. M. Kellogg, Department of Organic Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands
- 2320 Methylenation of Carbonyl Compounds: (+)-3-Methylene-cis-p-menthane
L. Lombardo, Research School of Chemistry, The Australian National University, G.P.O. Box 4 Canberra, A.C.T. 2601, Australia
- 2330 Preparation of Optically Pure (-)-8-Phenylmenthol
H. E. Ensley and J. F. Brausch, Department of Chemistry, Tulane University, New Orleans, LA 70118
- 2331 Acetone Trimethylsilyl Enol Ether
N. D. A. Walshe, G. B. T. Goodwin, G. C. Smith, and F. E. Woodward, Pfizer Central Research, Sandwich, Kent CT13, 9NJ, England

- 2334 t-Octyl-t-butylamine
E. J. Corey and A. W. Gross, Department of Chemistry, Harvard University, Cambridge, MA 02138
- 2336 Preparation and Inverse Electron Demand Diels-Alder Reaction of an Electron-Deficient Diene: Methyl 2-Oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate
D. L. Boger and M. D. Mullican, Department of Medicinal Chemistry, The University of Kansas, Lawrence, KS 66045

CUMULATIVE AUTHOR INDEX
FOR VOLUMES, 60, 61, 62 and 63

This index comprises the names of contributors to Volumes 60, 61, 62 and 63 only. For authors to previous volumes, see cumulative indices in Volume 59, which covers Volumes 55 through 59, and Volume 54, which covers Volumes 50 through 54, and either indices in Collective Volumes I through V or single volumes entitled *Organic Syntheses*, *Collective Volumes*, I, II, III, IV, V, *Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

- | | |
|---|--|
| <p>Aebi, J., 63, 109
 Albin, A., 61, 98
 Alderdice, M., 62, 14
 Alexakis, A., 62, 1
 Anderson, A. G., 60, 34
 Anello, L. B., 63, 154</p> <p>Bach, R. D., 60, 63
 Bal, B., 63, 89
 Balderman, D., 60, 104
 Banner, B. L., 63, 127
 Barnier, J. P., 60, 25
 Bastiaansen, L. A. M., 60, 72
 Batcho, A. D., 63, 214
 Bauer, M., 61, 35
 Beadle, J. R., 62, 179
 Berlin, K. D., 61, 56
 Bettinetti, G. F., 61, 98
 Blacklock, T. J., 60, 53
 Böhm, I., 60, 41
 Bond, F. T., 61, 141
 Branca, S. J., 61, 65
 Brown, H. C., 61, 104
 Buchschacher, P., 63, 37
 Buntin, S. A., 61, 82
 Buse, C. T., 63, 79, 89</p> <p>Cahiez, G., 62, 1
 Caldwell, W. E., 62, 118
 Cargill, R. L., 62, 118
 Carozza, L., 63, 127
 Cassady, J. M., 61, 77
 Chadha, N. K., 63, 44</p> | <p>Chamberlin, A. R., 61, 141
 Champion, J., 60, 18, 25
 Chan, D. M. T., 62, 58
 Chan, W. K., 61, 48, 134
 Chang, V. S., 60, 11
 Chatziosifidis, I., 62, 95
 Chiu, I-C., 61, 59
 Citterio, A., 62, 67
 Clausen, K., 62, 158
 Cohen, N., 63, 127
 Conia, J. M., 60, 18, 25
 Crabbe, P., 63, 203
 Crass, G., 61, 24
 Crossland, I., 60, 6</p> <p>Dalton, J. R., 62, 118
 Danishefsky, S., 60, 66, 61, 147
 Denis, J. M., 60, 18
 Dessau, R. M., 61, 22
 DiBiase, S. A., 62, 179
 Dittmer, D. C., 62, 210</p> <p>Earl, R. A., 60, 81
 Ellis, M. K., 63, 140
 Exon, C. M., 63, 66</p> <p>Fahrni H. P., 63, 175
 Farrand, R., 61, 71
 Fishel, D. I., 61, 8
 Fleming, M. P., 60, 113
 Fry, J. L., 60, 108
 Fung, A. P., 63, 188
 Fürst, A., 63, 37</p> |
|---|--|

Gassman, P. G., 60, 14
 Gawley, R. E., 63, 136
 Georgiadis, G. M., 61, 74
 Gerlach, F., 63, 192
 Ghosh, S., 62, 125
 Giesecke, H., 60, 49
 Gilow, H. M., 62, 111
 Godofroi, E. F., 60, 72
 Gokel, G. W., 62, 179
 Golding, B. T., 63, 140
 Graham, R. S., 63, 57
 Gras, J. L., 60, 88
 Gringore, O. H., 63, 121
 Guaciaro, M. A., 61, 65
 Gunn, B. P., 61, 59

Hafner, K., 62, 134
 Hajos, Z. G., 63, 26
 Hamada, Y., 62, 191
 Hansen, H.-J., 62, 202
 Hartmann, W., 62, 149
 Harvey, R. G., 62, 165
 Hashimoto, K., 61, 122
 Hayashi, J., 62, 86
 Heathcock, C. H., 63, 79, 89, 99
 Heck, R. F., 61, 82
 Hegedus, L. S., 62, 48
 Heiba, E. I., 61, 22
 Heilman, S. M., 62, 196
 Heimbach, H., 62, 95
 Heine, H.-G., 62, 149
 Helquist, P., 62, 74
 Herranz, E., 61, 85, 93
 Hidber, A., 61, 42
 Hill, J. G., 63, 66
 Hocker, J., 60, 49
 Hoffman, R. V., 60, 121
 Höfle, G., 61, 14
 Holden, M. S., 62, 48
 Holly, F. W., 63, 171
 Hopf, H., 60, 41
 Hosomi, A., 62, 86
 House, H. O., 62, 101
 Howie, G. A., 61, 77
 Hühner, F., 62, 95
 Hull, R., 61, 71

Ireland, R. F., 61, 116

Jakiela, D. J., 62, 74
 Jakovac, I. J., 63, 10
 Jones, II, G., 62, 111
 Jones, J. B., 63, 10
 Jones, L. D., 62, 74

Jones, M., Jr., 61, 129

Kalinowski, H.-O., 61, 24
 Kalir, A., 60, 104
 Kane, V. Y., 61, 129
 Keith, D. R., 62, 140
 Keller, O., 63, 160
 Keller, W. C., 63, 160
 King, B. T., 62, 140
 Kitahara, T., 61, 147
 Kleinschroth, J., 60, 41
 Knight, J. W., 60, 63
 Kogure, T., 63, 18
 Konieczny, M., 62, 165
 Korn, A., 61, 65
 Kozyrod, R. P., 62, 24
 Kropp, P. J., 61, 112
 Krumpolz, M., 60, 20
 Kuhlmann, H., 62, 170
 Kuwajima, I., 61, 122

Lamb, S. E., 60, 11
 Lang, R. W., 62, 202
 Lange, B., 61, 14
 Langer, W., 61, 24
 Lawesson, S.-O., 62, 158
 Lee, D. G., 60, 11
 Leimgruber, W., 63, 214
 Lienhard, U., 63, 175
 Liotta, E. L., 61, 141
 Little, R. D., 61, 17
 Livinghouse, T., 60, 126
 Lusch, M. J., 62, 101

Marguerite, J., 63, 147
 Martin, D., 61, 35
 Masamune, S., 61, 48, 134
 Matsumura, Y., 63, 206
 Matsushita, H., 62, 31
 McKearin, J. M., 62, 48
 McMurry, J. E., 60, 113
 Meinhardt, K.-P., 62, 134
 Midland, M. M., 63, 57
 Minoli, G., 61, 98
 Miyachita, M., 60, 101, 117
 Montgomery, S. H., 63, 99
 Morton, G. H., 62, 118
 Murahashi, S.-I., 62, 39

Nagashima, H., 62, 9
 Nakamura, E., 61, 122
 Nanninga, T. N., 62, 58
 Naota, T., 62, 39
 Nassim, B., 63, 203

Negishi, E.-I., 61, 104; 62, 31
Neises, B., 63, 183
Nemoto, H., 62, 9
Neubert, M. E., 61, 8
Neuenschwander, M., 63, 175
Nomura, G. S., 62, 101
Normant, J. F., 62, 1

O'Donnell, D. J., 61, 56
Oertle, K., 63, 192
Oikawa, Y., 63, 198
Ojima, I., 63, 18
Olah, G. A., 63, 188
O'Neil, T. H., 61, 116
Orfanopoulos, M., 60, 108
Ottenheim, H. C. J., 61, 1

Padwa, A., 60, 53
Paleveda, W. J., 63, 171
Paquette, L. A., 61, 39
Parrish, D. R., 63, 26
Partridge, J. J., 63, 44
Peters, R. H., 60, 92
Phillips, W. V., 62, 101
Pinhey, J. T., 62, 24
Pirrung, M. C., 63, 99
Pulwer, M. J., 60, 53

Ramalingam, K., 61, 56
Ramarajan, K., 61, 56
Rasmussen, J. K., 62, 196
Reetz, M. T., 62, 95
Regenye, R., 63, 66
Robert-Lopes, M.-T., 63, 203
Robinson, J. M., 61, 77
Roczek, J., 60, 20
Rodewald, P. G., 61, 22
Rouessac, F. P., 63, 121

Sakurai, H., 62, 86
Salaün, J., 63, 147
Salomon, R. G., 62, 125
Scheibye, S., 62, 158
Scholz, K.-H., 62, 149
Schuda, P. F., 61, 147
Sedergran, T. C., 62, 210
Seebach, D., 61, 24, 42; 63, 1, 109
Shama, S. A., 61, 62
Sharpless, K. B., 60, 29;
61, 85, 93; 63, 66
Shioiri, T., 62, 187, 191
Shono, T., 63, 206
Sieloff, R. F., 62, 101
Silverman, S. B., 60, 108

Singh, R. K., 60, 66
Skulnick, H. I., 61, 5
Smith, A. B., III, 61, 65
Smith, G. A., 63, 136
Smith, K., 63, 89
Spessard, G. O., 61, 48, 134
Stamos, I. K., 61, 77
Stang, P. J., 60, 34
Steglich, W., 63, 183
Stetter, H., 62, 170
Stowell, J. C., 62, 140
Sugano, K., 63, 198
Sum, F. W., 62, 14
Sutter, M. A., 63, 1

Taber, D. F., 61, 59
Talley, J. J., 60, 14
Tanabe, M., 60, 92
Tanigawa, Y., 62, 39
Taylor, R. T., 61, 39
Thalmann, A., 63, 192
Thomsen, I., 62, 158
Tijhuis, M. W., 61, 1
Tise, F. P., 61, 112
Tolman, G. L., 61, 116
Townsend, L. B., 60, 81
Trost, B. M., 62, 58
Tsubata, K., 63, 206
Tsuji, J., 62, 9

Umbreit, M., 60, 29
Uskokovic, M. R., 63, 44

Van Der Puy, M., 63, 154
Van Lier, P. M., 60, 72
van Look, G., 63, 160
Veber, D. F., 63, 171
Venegas, M. G., 61, 17

Wamser, C. C., 61, 62
Wasmuth, D., 63, 109
Weber, R. H., 63, 1
Weiler, L., 62, 14
Wersin, G., 63, 160
White, D. A., 60, 1, 58, 78
Wierenga, W., 61, 5
Wilka, E.-M., 61, 24
Williams, A. L., 61, 22
Wilson, S. R., 61, 74
Wovkulich, P. M., 61, 65

Yamada, S.-I., 62, 187
Yanami, T., 60, 101, 117
Yoda, Y., 63, 18

Yonemitsu, O., **63**, 198
Yoshikoshi, A., **60**, 101, 11/
Yoshioka, T., **63**, 198

Young, S. D., **63**, 79

Züger, M. F., **63**, 1

CUMULATIVE SUBJECT INDEX
FOR VOLUMES 60, 61, 62, AND 63

This index comprises subject matter for Volumes 60, 61, 62, and 63 only. For subjects in previous volumes, see the cumulative indices in Volume 59, which covers Volumes 55 through 59, and Volume 54, which covers Volumes 50 through 54, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in brackets. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

ACETAMIDE, N-(2,4-DIFORMYL-5-HYDROXYPHENYL)- [67149-23-9], **60**, 49
 Acetamide, N-[2,4-bis(1,3-diphenyl-2-imidazolidinyl)-5-hydroxyphenyl]-
 [67149-22-8], **60**, 50
 Acetamide, N-(3-hydroxyphenyl)- [621-42-1], **60**, 49
 Acetamidic acid, N-(trimethylsilyl)-, trimethylsilyl ester, **63**, 88
 3-Acetamidophenol [621-42-1], **60**, 49
 Acetic acid [64-19-7], **61**, 22; **62**, 15, 165
 Acetic acid-2-¹³C [1563-80-0], drying of, **60**, 97
 Acetic acid anhydride [108-24-7], **61**, 22
 Acetic acid, bromo-, ethyl ester [105-36-2], **61**, 122
 Acetic acid, bromo-, methyl ester [96-32-2], **63**, 56
 Acetic acid, diphenyl- [117-34-0], **61**, 45
 Acetic acid, lead (4+) salt [546-67-8], **62**, 30
 Acetic acid, manganese(2+) salt, tetrahydrate [6156-78-1], **61**, 22
 Acetic acid, [3,4-(methylenedioxy)phenyl]- [2861-28-1], **62**, 77
 Acetic acid, (1-methylethenyl)ester, **60**, 67
 Acetic acid, palladium(2+) salt [3375-31-3], **61**, 82
 Acetic acid, phenylacetyl-, methyl ester, **63**, 202
 Acetic acid, trifluoro-, mercury(2+) salt [13257-51-7], **61**, 48
 ACETIC ACID, (TRIMETHYLSILYL)-, ETHYL ESTER [4071-88-9], **61**, 122
 Acetic acid (triphenylphosphoranylidene)-, ethyl ester [1099-45-2], **62**, 209
 Acetoacetic acid, ethyl ester, **63**, 9
 Acetone cyanohydrin [75-86-5], **60**, 127
 Acetone, dimethyl acetal, **63**, 135
 Acetonitrile [75-05-8], **62**, 186
 Acetonitrile, 2-(tert-butoxycarbonyloxyimino)-2-phenyl-, **63**, 171
 Acetonitrile, cyclohexylidene [4435-18-1], **62**, 179

ACETOXY BROMIDES, VICINAL, **63**, 140
 2-Acetoxy-1-bromopropane, (S)-(-)-, **63**, 141
 2-(Acetoxymethyl)allyltrimethylsilane [72047-94-0], **62**, 64, 66
 p-Acetylbenzonitrile cyanohydrin, **60**, 17
 Acetyl chloride, phenyl-, **63**, 202
 3-Acetyl-5-chloro-2-oxazolidinone [60759-48-0], **62**, 151
 1-Acetylcyclopropanecarboxylic acid, **60**, 69
 4-Acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one [65948-43-8],
62, 152
 1-Acetyl-2-methylcyclohexene, **62**, 19
 3-Acetyl-2-oxazolidinone [1432-43-5], **62**, 150
 3-Acetyl-2(3H)-oxazolone [60759-49-1], **62**, 151
 Acetylation, of 2-oxazolidinone, **62**, 149
 Acetylene [74-86-2], **62**, 2
 Acetylenes, homologation to allenes, **63**, 203
 Acetylenes, in peptide synthesis, **63**, 175
 α,β -ACETYLENIC KETONES, ASYMMETRIC REDUCTION OF, **63**, 57
 ACID CHLORIDES FROM α -KETO ACIDS, **61**, 1
 Acrolein [107-02-8], **62**, 140
 ACRYLIC ACID, 2-(BROMOMETHYL)-, METHYL ESTER [4224-69-5], **61**, 77
 Acyclic enol phosphates, **62**, 19
 Acylation, of ethyl (triphenylphosphoranylidene)acetate, **62**, 202
 ACYLOIN CONDENSATION BY THIAZOLIUM ION CATALYSIS, **62**, 170
 Acyloins, table of, **62**, 177
 2-Adamantanone [700-58-3], **60**, 105, 113
 ADAMANTYLIDENEADAMANTANE [30541-56-1], **60**, 113

Adenosine 5'-(trihydrogen diphosphate), 5' + 5' ester with 3-(aminocarbonyl)-
 alcohol dehydrogenase, **63**, 17

Adogen 464 [50934-77-5], **60**, 11

Alanine, L-, N-carboxybenzyl ester, **63**, 182

ALANINE, PHENYL-, N-tert-BUTOXYCARBONYL-, L-, **63**, 160

Alanine, N-[(phenylmethoxy)carbonyl]-, L- [1142-20-7], **63**, 182

Alcohols, alkynyl-, synthesis of, **63**, 61

Alcohols, amino-, by reduction of acids, **63**, 138

Aldol condensation, intramolecular, asymmetric, **63**, 26, 37

Aldol condensation, diastereoselective, **63**, 94, 104

ALIPHATIC β -KETOESTERS, **61**, 5

Alkene photodimerization, **62**, 125

Alkenes, amination with palladium(II) catalysis, **62**, 48

Alkenyl iodides from alkenyl-copper derivatives, **62**, 1

ALKOXIDE ENOLATES, **63**, 100

α -ALKYLATION, DIASTEREOSELECTIVE, **63**, 109

α -tert-ALKYLATION OF KETONES, **62**, 95

4-ALKYLBENZOYL CHLORIDES. **61**. 8

β -Alkyl- α,β -unsaturated esters, **62**, 21

β -ALKYL- α,β -UNSATURATED ESTERS FROM ENOL PHOSPHATES OF β -KETO ESTERS,
62, 14

Alkynyl alcohols, synthesis of, **63**, 61

Allenes, from Wittig reagents and acid chlorides, **62**, 202

Allenes, synthesis, from acetylenes, **63**, 204

α -ALLENIC ESTERS FROM α -PHOSPHORANYLIDENE ESTERS AND ACID CHLORIDES:
 ETHYL 2,3-PENTADIENOATE, **62**, 202

α -Allenic esters, table of, **62**, 202

Allyl anion synthon, **62**, 64

Allyl bromide [106-95-6], **62**, 49; **63**, 120

Allylation, of isobutyraldehyde, **62**, 125

ALLYLIC ALCOHOLS, ENANTIOSELECTIVE EPOXIDATION, **63**, 66

ALLYLTRIALKYLSILANE, CONJUGATION ADDITION TO α,β -UNSATURATED KETONES, **62**, 86

Allyltrimethylsilane [762-72-1], **62**, 86

Aluminate(1-), tetrahydro-, lithium, [16853-85-3], **61**, 42

Aluminum chloride [7446-70-0], **61**, 8

Aluminum, trimethyl- [75-24-1], **62**, 38

Amides, preparation of, **63**, 178

Amination, of alkenes with palladium(II) catalysis, **62**, 48

Amine, diisopropyl-, **61**, 116; **63**, 81, 89, 203

Amines. by displacement of hydroxyl with phthalimide. **62**, 48

Amines from tertiary alcohols, table, **60**, 107

AMINO ACIDS, tert-BUTOXYCARBONYLATION OF, **63**, 160, 171

α -Amino acids, esterification of, **63**, 185

Amino acids, reduction to amino alcohols, **63**, 138

Amino alcohols, by reduction of amino acids, **63**, 138

m-Aminobenzotrifluoride [98-16-8], **60**, 121

6-Amino-3,4-dimethyl-cis-3-cyclohexen-1-ol [65948-45-0], **62**, 152

2-Aminoethanol [141-43-5], **62**, 150

5-Aminotetrazole [4418-61-5], **61**, 14

5-Aminotetrazole monohydrate [15454-54-3], **61**, 14

Ammonium, benzyltriethyl-, chloride [56-37-1], **61**, 24, 85

Ammonium, tetrabutyl-, fluoride, hydrate [22206-57-1], **61**, 122

Ammonium, tetrabutyl-, hydroxide [2052-49-5], **61**, 122

Ammonium, tetraethyl-, p-toluenesulfonate, **63**, 207

ANDROSTANOLONE [521-18-6], **61**, 116

ANDROSTAN-3-ONE, 17-HYDROXY-, (5 α , 17 β)- [521-18-6], **61**, 116

5 α -ANDROSTAN-3-ONE. 17 β -HYDROXY- [521-18-6], **61**, 116

ANDROST-2-EN-17-OL, (5 α , 17 β)- [2639-53-4], **61**, 116

5 α -ANDROST-2-EN-17 β -OL [2639-53-4], **61**, 116

Aniline, **60**, 68

Aniline, N,N-dimethyl- [121-69-7], **62**, 40

p-Anisaldehyde [123-11-5], **62**, 196

o-Anisic acid [579-75-9], **61**, 59

Anisole [100-66-3], **62**, 24, 158

ANODIC OXIDATION, **63**, 206

ANODIC OXIDATION OF ACIDS, **60**, 1

Araboascorbic acid, **63**, 130

Aromatic hydrocarbons, by reduction of quinones, **62**, 165

AROMATIC β -KETOESTERS, **61**, 5

ARYLATION OF β -DICARBONYL COMPOUNDS, **62**, 24

Aryllead derivatives, reaction with β -ketoesters, **62**, 24

Aryllead triacetate, **62**, 27

Aryl lithium, addition to nitriles, **62**, 74

Aryl radicals, addition to electron-deficient alkenes, **62**, 67

Aryl radicals, from reduction of diazonium salts, **62**, 67

Arylsulfonyl chlorides, table, **60**, 124

ASYMMETRIC HYDROGENATION, of ketopantoyl lactone, **63**, 18

ASYMMETRIC SOLVENT INDUCTIONS, **61**, 24

ATROPALDEHYDE [4432-63-7], **60**, 6

Atropaldehyde diethyl acetal, **60**, 7

13-Azabicyclo[7.3.1]tridecan-5-ol, stereoisomer [61714-12-3], **61**, 108

Azaindoles, synthesis of, **63**, 219

Azetidinecarboxylic acid, (S)-(-)-, **63**, 33

Azide anion, substitution for chloride, **62**, 187

2-Azido-2-phenyladamantane [65218-96-4], **60**, 104

2(1H) Azocinone, hexahydro [673-66-5], **63**, 188

AZULENE [275-51-4], **62**, 139

Benzalacetone [122-57-6], **62**, 86

Benzaldehyde [100-52-7], **61**, 42; **62**, 180

Benzaldehyde, 4-methoxy- [123-11-5], **62**, 196

Benzamidine hydrochloride [1670-14-0], **60**, 53

Benz[a]anthracene [56-55-3], **62**, 169

Benz[a]anthracene-7-12-dione [2498-66-0], **62**, 169

Benzenamine, N,N-dimethyl- [121-69-7], **62**, 40

Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)- [70197-43-2],
62, 47

Benzenamine, N-methyl-, trifluoroacetate [29885-95-8], **60**, 88

Benzenamine, 3-(trifluoromethyl)- [98-16-8], **60**, 121

Benzene, (2-bromoethenyl)- (Z)- [588-73-8], **62**, 47

Benzene, 1-chloro-2,4-dinitro- [97-00-7], **62**, 139

Benzene, (chloromethyl)- [100-44-7], **62**, 178; **63**, 225

Benzene, 1,1'-(1-chloro-3-methylcyclopropane-1,2-diyl)bis-, **60**, 56

Benzene, (2,2-dichlorocyclopropyl)- [2415-80-7], **60**, 6

Benzene, (2,2-diethoxycyclopropyl)-, **60**, 8

Benzene, 1,1'-(1,2-ethenediyl)bis-, (E)- [103-30-0], **61**, 85, 93

Benzene, 1-ethyl-3-nitro- [7369-50-8], **60**, 108

Benzene, hexamethyl- [87-85-4], **61**, 98
 Benzene, iodo- [591-50-4], **61**, 82
 BENZENE, (ISOCYANOMETHYL)- [10340-91-7], **61**, 14
 Benzene, methoxy- [100-66-3], **62**, 30, 164
 BENZENE, 1,1'-(3-METHYL-1-CYCLOPROPENE-1,2-DIYL)BIS- [51425-87-7], **60**, 53
 Benzene, 1-methyl-4-(1-methyl-ethyl)- [99-87-6], **62**, 133
 Benzene, 2-methyl-1-nitro-3-(phenylmethoxy)- [20876-37-3], **63**, 225
 Benzene, pentyl [538-68-1], **61**, 8
 Benzene, 1-propenyl-(E)- [873-66-5], **60**, 54
 BENZENEACETALDEHYDE, α -METHYLENE [4432-63-7], **60**, 6
 Benzeneacetic acid, α -phenyl [117-34-0], **61**, 42
 Benzeneacetonitrile, α -[[[1,1-dimethylethoxy)carbonyl]oxy]imino]-
 [58632-95-3], **63**, 174
 BENZENEACETONITRILE, α -HYDROXY- α -PHENYL [4746-48-9], **60**, 14
 Benzeneacetonitrile, 4-methoxy- α -[(trimethylsilyl)oxy]- [66985-48-6], **62**, 196
 Benzeneacetyl chloride [103-80-0], **63**, 202
 Benzenebutanoic acid, β -oxo-, methyl ester [37779-49-0], **63**, 202
 Benzenecarboximidamide monohydrochloride [1670-14-0], **60**, 53
 1,4-Benzenediol [123-31-9], **62**, 157
 Benzenemethanaminium, N,N,N-triethyl-, chloride [56-37-1], **60**, 7, 68;
61, 24, 85
 BENZENEMETHANOL, α -BUTYL- [583-03-9], **61**, 42
 BENZENEMETHANOL, α -BUTYL-, (R)- [19641-53-3], **61**, 42
 BENZENEPROPANAL, α -METHYL- [5445-77-2], **61**, 82
 Benzenepropanoic acid, α,β -dibromo, (R*,S*)- [31357-31-0], **62**, 47
 Benzenesulfonamide, N-chloro-4-methyl-, sodium salt, trihydrate [7080-50-4],
61, 85

BENZENESULFONAMIDE, N-(2-HYDROXYCYCLOHEXYL)-4-METHYL-, cis- [58107-40-7],

61, 85

Benzenesulfonamide, 4-methyl-N-[2-(2-propenyl)cyclopentyl], cis-

[81097-06-5], **62, 57**

Benzenesulfonic acid, 2,4,6-tris(1-methylethyl)-, hydrazide [39085-59-1],

61, 141

Benzenesulfonyl chloride, 4-methyl- [98-59-9], **62, 57**

BENZENESULFONYL CHLORIDE, 3-(TRIFLUOROMETHYL)- [777-44-6], **60, 121**

1,3-Benzodioxole-5-acetic acid [2861-28-1], **62, 85**

Benzoic acid, **60, 13**

Benzoic acid, 2-methoxy- [579-75-9], **61, 59**

Benzonitrile [100-47-0], **62, 85**

Benzophenone [119-61-9], **60, 15**

BENZOPHENONE CYANOHYDRIN [4746-48-9], **60, 14**

Benzophenone, sodium ketyl, **62, 77**

p-Benzoquinone [106-51-4], **60, 128; 62, 57**

p-Benzoquinone monotrimeethylsilyl cyanohydrin [40861-57-2], **60, 126**

3,1-BENZOXAZEPINE [15123-59-8], **61, 98**

2(3H)-Benzoxazolone, 3-acetyl-3a,4,7,7a-tetrahydro-5,6-dimethyl-

[65948-43-8], **62, 157**

Benzoyl chloride, **60, 73**

BENZOYL CHLORIDE, 4-PENTYL- [49763-65-7], **61, 8**

1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole [62457-77-6], **60, 73**

Benzyl bromide, **60, 93**

Benzyl chloride [100-44-7], **62, 171; 63, 214**

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride [4568-71-2],

62, 171

BENZYL ISOCYANIDE [10340-91-7], 61, 14
 4-Benzyloxy-2-butanone [6278-91-7], 60, 93
 5-Benzyloxy-3-hydroxy-3-methylpentanoic acid 2 ¹³C [57930-65-6], 60, 94
 4-BENZYLOXYINDOLE, 63, 214
 Benzyltriethylammonium chloride [56-37-1], 61, 24, 85
 Bicyclo[7.3.0]dodecane-1.5-diol [52318-91-9], 61, 108
 Bicyclo[3.2.0]heptan-2-ol, 3,3-dimethyl- [71221-67-5], 62, 133
 Bicyclo[3.2.0]heptan-2-one, 3,3-dimethyl- [71221-70-0], 62, 125, 133
 Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-, (1R)- [464-49-3], 61, 141
 Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (1S)- [7785-26-4], 63, 56
 Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (1R)- [7785-70-8], 63, 65
 BICYCLO[4.1.0]HEPT-3-ENE, 7,7-DIBROMO-1,6-DIMETHYL- [38749-43-8], 61, 39
 BICYCLO[2.2.0]HEXA-2,5-DIENE, 1,2,3,4,5,6-HEXAMETHYL [7641-77-2], 61, 62
 Bicyclo[4.2.0]octan-2-one, 6-methyl- [13404-66-5], 62, 118
 2,2'-Bi-1H-imidazole, 1,3-dibenzoyl-2,3-dihydro-, monohydrochloride
 [65276-00-8], 60, 74
 2,2'-Bi-1H-imidazole, 1,1',3-tribenzoyl-2,3-dihydro- [62457-77-6], 60, 73
 2,2'-Bipyridine [366-18-7], 61, 5, 65
 2,2'-Bipyridyl [366-18-7], 61, 5, 65
 BIRCH REDUCTION, 61, 59
 Bis(copper(I) trifluoromethanesulfonate)benzene complex [37234-97-2],
 62, 127
 1,4-BIS(DIMETHYLAMINO)-2,3-DIMETHOXYBUTANE, (S,S)-(+)-, [DDB] [26549-21-3],
 61, 24, 42
 N-[2,4,-Bis(1,3-Diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide
 [67149-22-8], 60, 50

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide

[19172-47-5], **62**, 158

BIS(2,2,2-TRICHLOROETHYL)AZODICARBOXYLATE [38857-88-4], **61**, 17

1,2-bis(Trimethylsiloxy)-cyclobutene, **60**, 19

BOC-ON (Aldrich), **63**, 172

9-Borabicyclo[3.3.1]nonane [280-64-8], **63**, 58

9-Borabicyclo[3.3.1]nonane, 9-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)-

[73624-47-2], **63**, 65

Borane, compd. with thiobis[methane] (1:1) [13292-87-0], **63**, 139

Borane, di-3-pinanyl-, (+)-, **63**, 46

Borane-methyl sulfide complex, **63**, 136

Borane-tetrahydrofuran [14044-65-6], **61**, 103; **63**, 46

Borane, bis(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)-, [1 α ,2 α ,3 β

(1R*,2R*,3S*,5S*), 5 α]-(+)- [21947-87-5], **63**, 56

9b-BORAPHENALENE, DODECAHYDRO- [16664-33-8]; cis,cis-: (3 $\alpha\alpha$,6 $\alpha\alpha$,9 $\alpha\alpha$),

[1130-59-2]; cis,trans-: (3 $\alpha\alpha$,6 $\alpha\alpha$,9 $\alpha\beta$), [2938-53-6], **61**, 103

Borate (1-), cyclododecane-1,5,9-triylhydro-, lithium [36005-35-3], **61**, 103

Borate (1-), 1,5,9-cyclododecane triylhydro-, lithium [36005-35-3], **61**, 103

Borate (1-), tetrahydro-, sodium [16940-66-2], **61**, 85

Boric anhydride-sulfuric acid scrubber, **60**, 110

Boron trifluoride butyl etherate, **60**, 27

Boron trifluoride etherate [109-63-7], **61**, 116; **62**, 195

BROMIDES, ACETOXY, VICINAL, **63**, 140

Bromination, selective, to remove β , γ -unsaturated nitrile, **62**, 179

Bromine [7726-95-6], **61**, 35; **62**, 78

β -Bromoacetals, preparation from acrolein. **62**, 140

Bromoacetate, ethyl, **62**, 203

4-Bromo-2-butanone [28509-46-8], **62**, 141, 148

2-BROMO-2-CYCLOPENTENONE [10481-34-2], **61**, 65

2-BROMOCYCLOPENTENONE ETHYLENE KETAL, **61**, 65

2-(2-Bromoethyl)-1,3-dioxane [33884-43-4], **62**, 140

Bromoform [75-25-2], **61**, 39

1-Bromoheptane [629-04-9], **61**, 59

β -Bromoketals, preparation from methyl vinyl ketone, **62**, 140

2-(2'-Bromo-4',5'-methylenedioxyphenyl)ethanol, **62**, 78

3-Bromopropanal, **62**, 141

3-Bromo-1-propene, **62**, 57; **63**, 111

β -Bromostyrene, (Z)- [588-73-8], **62**, 39

1,3-Butadiene, 2,3-dimethyl- [513-81-5], **62**, 157

Butanal [123-72-8], **62**, 117, 178

1-Butanaminium, N,N,N-tributyl-, perchlorate [1923-70-1], **60**, 58

1-Butanaminium, N,N,N-tributyl-, hydroxide [2052-49-5], **61**, 122

Butane, 1-bromo- [109-65-9], **61**, 141; **62**, 20

Butane, 2-chloro-2-methyl- [594-36-5], **62**, 100

BUTANEDIAMIDE, 2,3-DIHYDROXY-N,N,N',N'-TETRAMETHYL-, (R,R)- [26549-65-5],
61, 24, 42

BUTANEDIAMIDE, 2,3-DIMETHOXY-N,N,N',N'-TETRAMETHYL-, (R,R)- [26549-29-1],
61, 24, 42

1,4-BUTANEDIAMINE-2,3-DIMETHOXY-N,N,N',N'-TETRAMETHYL-, (S,S)-(+)-
[26549-21-3], **61**, 24, 42

Butanedioic acid, 2,3-dihydroxy-, (R-(R*,R*))-, diethyl ester [87-91-2]
63, 78

Butanedioic acid, 2,3-dihydroxy-, (S,S)- [147-71-7], **61**, 24

Butanedioic acid, hydroxy-, (S)-, diethyl ester [691-84-9], **63**, 120

Butanedioic acid, 2-hydroxy-3-(2-propenyl)-, (S-(R*,S*))-, diethyl ester
 [73837-97-5], **63**, 120

Butanenitrile, 2-(1-ethoxyethoxy)-, (R*,R*)- or (R*,S*)- [[72658-42-5] or
 [72658-43-6]], respectively, **63**, 88

Butanenitrile, 2-hydroxy- [4476-02-2], **63**, 87

1,2,3,4-BUTANETETRACARBOXYLIC ACID, TETRAETHYL ESTER [4373-15-3], **60**, 58

Butanoic acid, 3-hydroxy-, (S)-, ethyl ester [56816-01-4], **63**, 9

Butanoic acid, 3-oxo-, ethyl ester [141-97-9], **63**, 9

1-Butanol, 2-amino-3-methyl-, (S)- [2026-48-4], **63**, 139

2-Butanone, 4-bromo- [28509-46-8], **62**, 148

2-BUTANONE, 4-(4-CHLOROPHENYL)- [3506-75-0], **62**, 67

2-Butanone, 4-hydroxy- [590-90-9], **60**, 93

1-BUTANONE, 1-(1-METHYL-1-H-PYRROL-3-YL)- [62128-46-5], **62**, 117

2-Butanone, 4-phenylmethoxy- [6278-91-7], **60**, 93

2-Butenedioic acid, (E)-, diethyl ester [623-91-6], **60**, 58, 59

2-Butenedioic acid, (E)-, ethyl 1,1-dimethylethyl ester, **63**, 183

2-Butenedioic acid, (E)-, monoethyl ester [2459-05-4], **63**, 187

2-Butenoic acid, (E)-, ethyl ester [623-70-1], **61**, 85

3-Buten-2-one [78-94-4], **61**, 129; **62**, 73, 148; **63**, 36, 43

3-Buten-2-one, 4-methoxy- [4652-27-1], **61**, 147

3-Buten-2-one, 4-phenyl- [122-57-6], **62**, 94

1-Buten-3-yne [689-97-4], **62**, 31

tert-BUTOXYCARBONYLATION, AMINO ACIDS, **63**, 160, 171

tert-Butyl alcohol [75-65-0], **61**, 85

tert-BUTYL ETHYL FUMARATE, **63**, 183

tert-Butyl hydroperoxide, **63**, 66

2-BUTYLBORNENE, **61**, 141

Butyl bromide [109-65-9], **61**, 141; **62**, 4
 S-tert-BUTYL CYCLOHEXYLMETHANETHIOATE [54829-37-7], **61**, 48, 134
 S-tert-BUTYL ESTER OF CHOLIC ACID [58587-05-6], **61**, 134
 Butyllithium [109-72-8], **61**, 5, 42, 74, 116; **62**, 1, 8, 47, 66; **63**, 89, 100
 sec-Butyllithium [598-30-1], **61**, 141
 tert-Butyllithium, **62**, 85
 N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-
 methylpyrrolidine, (2S,4S)-, **63**, 18
 t-Butyl phenyl ketone cyanohydrin, **60**, 17
 2-Butyne [503-17-3], **61**, 62
 2-Butynedioic acid, dimethyl ester [762-42-5], **60**, 69
 2-BUTYNOIC ACID, 4-HYDROXY-, METHYL ESTER [31555-05-2], **60**, 81
 Butyraldehyde [123-72-8], **62**, 112, 170
 BUTYROIN [496-77-5], **62**, 170
 γ -BUTYROLACTONES, **61**, 22
 γ -BUTYROLACTONE- γ -CARBOXYLIC ACID, (S)-(+)-, **63**, 121
 Butyronitrile, 2-hydroxy-, **63**, 79
 3-BUTYROYL-1-METHYLPYRROLE [7072-66-8], **62**, 117

 Camphor, D- [464-49-3], **61**, 141
 Cannula, transfer and filtration of methyllithium, **62**, 101
 Cannula transfer at low temperatures, **62**, 2
 Carbamates, α -methoxylation of, **63**, 209
 Carbamic acid, ethyl ester [51-79-6], **61**, 93
 Carbamic acid chloro-, ethyl ester, sodium salt [17510-52-0], **61**, 93

CARBAMIC ACID (2-HYDROXY-1,2-DIPHENYLETHYL)-, (R*,R*)-, ETHYL ESTER

[73197-89-4], 61, 93

Carbanion, of acetonitrile, 62, 179

Carboalumination of alkynes, 62, 31

Carbocupration, 62, 5

Carbocupration of alkynes, 62, 1

Carbodiimide, dicyclohexyl-, 63, 183

[Carboethoxymethylene]triphenylphosphorane [1099-45-2], 62, 202

Carbometallation. 62. 33

Carbomethoxylation of Grignard reagent, 60, 86

Carbonochloridic acid, methyl ester [79-22-1], 60, 83; 63, 213

Carbonochloridic acid, 2,2,2-trichloroethyl ester [17341-93-4], 61, 17

Carbonothioic dichloride [463-71-8], 61, 71

Carbon tetrachloride [56-23-5], 61, 35

Carbon tetrachloride-dry ice slush bath, 62, 16

Carbonic acid, diethyl ester [105-58-8], 62, 157

Carbonic acid, dimethyl ester [616-38-6], 62, 23

Carbostyryl [493-62-9], 61, 101

CARBOXYLIC ACIDS FROM OXIDATION OF TERMINAL ALKENES, 60, 11

Carboxylic acids, α -hydroxy-, esterification of, 63, 105

Carboxylic acids, β -hydroxy-, stereoselective synthesis of, 63, 95

CARBOXYLIC ESTERS, β -HYDROXY-, DIASTEREOSELECTIVE α -ALKYLATION, 63, 109

CATALYSIS, OF THE ACYLOIN CONDENSATION BY THIAZOLIUM ION, 62, 170

Cerium(IV) sulfate, 62, 68

CHIRAL MEDIA, 61, 24

Chloramine-T trihydrate [7080-50-4], 61, 85

Chlorination, of 3-acetyl-2-oxazolidinone, 62, 149

Chlorination, of thietane 1,1-dioxide, **62**, 210

p-Chloroacetophenone cyanohydrin, **60**, 17

4-Chloroaniline, **62**, 69

N-CHLORO-N-ARGENTOCARBAMATES, **61**, 93

Chloro(1,5-cyclooctadiene)rhodium (I) dimer, **63**, 18

1-Chloro-2,4-dinitrobenzene [97-00-7], **62**, 139

1-Chloro-1,2-diphenyl-3-methylcyclopropane, (1S,2R,3S), **60**, 56

1-Chloro-1,2-diphenyl-3-methylcyclopropane, (1S,2S,3R), **60**, 56

2-Chloro-2-methylbutane [594-36-5], **62**, 100

9b-Chloroperhydrophenalene [52079-56-8], **61**, 103

4-(4-CHLOROPHENYL)PENTAN-2-ONE [3506-75-0], **62**, 67

CHLOROPHENYLCARBENE, **60**, 53

3-Chlorothietane 1,1-dioxide [15953-83-0], **62**, 211; **63**, 147

Chlorotrimethylsilane [75 77 4], **61**, 122, 147; **62**, 66, 100, 201; **63**, 147

CHOLANE-24-THIOIC ACID, 3,7,12-TRIHIDROXY-S-(1,1-DIMETHYLETHYL)ESTER,
(3 α ,5 β ,7 α ,12 α)- [58587-05-6], **61**, 134

Cholan-24-oic acid, 3,7,12-trihydroxy-, (3 α ,5 β ,12 α) [81-25-4], **61**, 134

Cholic acid [81-25-4], **61**, 134

Chromatography column, water-jacketed, **60**, 37

Chromium trioxide. **60**. 21

Cinnamaldehyde, **62**, 142

Cinnamic acid, (E)- [140-10-3], **62**, 41

CINNAMONITRILE [1885-38-7], **62**, 180

Clemmensen reaction, **60**, 111

Condensation, of acetonitrile with benzaldehyde, **62**, 179

Condensation, of acetonitrile with cyclohexanone, **62**, 179

Conjugate addition, of allyltrialkylsilanes, **62**, 86

Conjugate addition, of aryl radicals, **62**, 67
 Conjugate addition, of cuprates to enol phosphates, **62**, 14
 CONJUGATE ALLYLATION OF α,β -UNSATURATED KETONES WITH ALLYLSILANES, **62**, 86
 Copper, (μ -(benzene))bis(trifluoromethanesulfonato-O)di- [37234-97-2], **62**, 133
 Copper, carbocupration of alkynes, **62**, 1
 Copper (I)-catalyzed photocycloaddition, **62**, 125
 Copper chloride (CuCl) [7758-89-6], **61**, 122; **62**, 9
 Copper iodide [7681-65-4], **62**, 8
 Copper(I) iodide, **62**, 8
 o-Cresol, 3-nitro-, **63**, 225
 Crotonic acid, (E)-, ethyl ester [623-70-1], **61**, 85
 18-Crown-6-potassium cyanide complex, **60**, 129
 Crum Brown-Walker reaction, **60**, 4
 Cuprate conjugate addition, to enol phosphates, **62**, 14
 Cupric chloride, **62**, 10
 Cuprous bromide, **63**, 203
 Cuprous bromide-dimethyl sulfide complex, **62**, 1
 Cuprous chloride, **60**, 42, 121; **61**, 122
 CYANIC ACID, PHENYL ESTER [1122-85-6], **61**, 35
 CYANIC ACID ESTERS, **61**, 35
 1-Cyanocyclopropanecarboxylic acid, **60**, 69
 CYANOGEN BROMIDE [506-68-3], **61**, 35
 Cyanohydrins, **60**, 14, 17
 Cyanosilylation, **60**, 15, 126; **62**, 196
 table, **60**, 131; **62**, 200
 In Situ CYANOSILYLATION OF CARBONYL COMPOUNDS: O-TRIMETHYLSILYL-
 4-METHOXYMANDELONITRILE [66985-48-6], **62**, 196

Cyclobuta-[f]-1,3-benzodioxole, 5,6-dihydro- [61099-23-8], **62**, **74**, **85**

Cyclobutane formation, **62**, **125**

1,2-Cyclobutanediol, cis [35358-33-9], **60**, **26**

1,2-Cyclobutanediol, trans [35358-34-0], **60**, **26**

1,2-CYCLOBUTANEDIONE [33689-28-0], **60**, **18**

Cyclobutanol [2919-23-5], **60**, **22**

CYCLOBUTANONE [1191-95-3], **60**, **20**

Cyclododecanone [830-13-7], **61**, **74**; **62**, **195**

1,5,9-Cyclododecatriene [4904-61-4], **61**, **103**

CYCLODODECENE [1501-82-2]

[*(E)*-1486-75-5, (*Z*)-1129-89-1], **60**, **29**

trans-CYCLODODECENE [1486-75-5], **60**, **29**

trans-Cyclododecene oxide [4683-60-7], **60**, **31**

CYCLODODECYL MERCAPTAN, **61**, **74**

Cycloheptanone [502-42-1], **63**, **188**

2,5-Cyclohexadiene-1-carbonitrile, 4-oxo-1-[(trimethylsilyl)oxy]-
[40861-57-2], **60**, **126**

1,4-Cyclohexadiene, 1,2-dicarbonitrile, 4,5-dichloro-3,6-dioxo-
[84-58-2], **61**, **129**

1,4-Cyclohexadiene, 1,2-dimethyl- [17351-28-9], **61**, **39**

2,5-Cyclohexadiene-1,4-dione [106-51-4], **60**, **128**; **62**, **57**

Cyclohexanamine, N,N'-methanetetraylbis- [538-75-0], **63**, **187**

Cyclohexane, cis-1,2-bis(hydroxymethyl)-, **63**, **10**

CYCLOHEXANE, 1-METHOXY-1-METHYL-4-(1-ETHENYL-1-METHYL)-, cis- [24655-71-8],
61, **112**

CYCLOHEXANE, 1-METHOXY-1-METHYL-4-(1-ETHENYL-1-METHYL)-, trans-
[24655-72-9], **61**, **112**

CYCLOHEXANECARBOETHIOIC ACID, S-(1,1-DIMETHYLETHYL) ESTER [54829-37-7],

61, 48, 134

Cyclohexanecarboxylic acid [98 89 5], **61, 134**

CYCLOHEXANECARBOXYLIC ACID, tert-BUTYL ESTER [16537-05-6], **61, 48**

CYCLOHEXANECARBOXYLIC ACID, 1,1-DIMETHYLETHYL ESTER [16537-05-6], **61, 48**

Cyclohexanecarboxylic acid, 2-oxo-, ethyl ester [1655-07-8], **62, 30**

Cyclohexanecarboxylic acid, 2-oxo-, methyl ester [41302-34-5], **62, 23**

1,2-Cyclohexanedimethanol, cis- [15753-50-1], **63, 17**

1,3-Cyclohexanedione [504-02-9], **61, 59**

1,3-Cyclohexanedione, 2-methyl- [1193-55-1], **63, 37**

1,3-Cyclohexanedione, 2-methyl-2-(3-oxobutyl)- [5073-65-4], **63, 37**

Cyclohexanone [108-94-1], **62, 15, 186**

CYCLOHEXANONE, 2-(2-OXOPROPYL)- [6126-53-0], **60, 117**

Cyclohexanone cyanohydrin, **60, 17**

Cyclohexene [110-83-8], **61, 85**

CYCLOHEXENE, 1-METHYL-4-(1-METHYLETHENYL)- [5989-27-5], **61, 112**

$\Delta^{1,\alpha}$ -Cyclohexeneacetonitrile [4435-18-1], **62, 186**

1-Cyclohexene-1-carboxylic acid, 2-[(diethoxyphosphinyl)oxy]-, methyl ester
[71712-64-6], **62, 23**

1-Cyclohexene-1-carboxylic acid, 2-methyl-, methyl ester [25662-38-3], **62, 14**

3-Cyclohexen-1-ol, 6-amino-3,4-dimethyl-, cis- [65948-45-0], **62, 152**

2-Cyclohexen-1-one, 3-methyl- [1193-18-6], **62, 124**

Cyclohex-2-en-1-one, photocycloaddition to ethylene, **62, 118**

CYCLOHEXYLIDENEACETONITRILE [4435-18-1], **62, 179**

Cyclooctanecarboxaldehyde [6688-11-5], **61, 129**

Cyclooctanone cyanohydrin, **60, 17**

Cyclooctene [931-88-4], **61**, 85
 Cyclooctene, (Z)- [931-87-3], **60**, 63
 cis-Cyclooctene [931-87-3], **60**, 63
 cis-CYCLOOCTENE OXIDE [4925-71-7], **60**, 63
 3a,7(1H)-Cyclopentacyclononenediol, decahydro- [52318-91-9], **61**, 108
 2,4-Cyclopentadiene-1-acetic acid, methyl ester [37455-98-4], **63**, 56
 CYCLOPENTADIENES, ASYMMETRIC HYDROBORATION, **63**, 44
 Cyclopentadiene, preparation of, **63**, 44
 Cyclopentadienide, sodium, **62**, 134; **63**, 45
 Cyclopentanamine, 2-(2-propenyl)-, cis- [81097-02-1], **62**, 57
 1,3-Cyclopentanedione, 2-methyl- [765-69-5], **63**, 26
 1,3-Cyclopentanedione, 2-methyl-2-(3-oxobutyl)- [25112-78-1], **63**, 26
 Cyclopentanol, 2-(2-propenyl)-, trans- [74743-89-8], **62**, 57
 Cyclopentanone [120-92-3], **62**, 100
 CYCLOPENTANONE, 2-(tert-PENTYL-) [25184-25-2], **62**, 95
 CYCLOPENTA[b]PYRROLE, 1,3a,4,5,6,6a-HEXAHYDRO-2-METHYL-1-[(4-METHYLPHENYL)-
 SULFONYL]-, cis- [81097-07-6], **62**, 48
 2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)-
 [49825-99-2], **63**, 44
 Cyclopentene oxide [285-67-6], **62**, 49
 3-Cyclopenten-1-ols, trans-2-alkyl-, synthesis of, **63**, 51
 2-Cyclopentenone [930-30-3], **61**, 65
 2-CYCLOPENTEN-1-ONE, 2-BROMO- [10481-34-2], **61**, 65
 Cyclopropane, 1-ethoxy-1-trimethylsiloxy-, **63**, 147
 CYCLOPROPANECARBOXALDEHYDE [1489-69-6], **60**, 25
 Cyclopropane-1,1-dicarboxylic acid [598-10-7], **60**, 67

Cyclopropanemethanol [2516-33-8], **60**, 21
 Cyclopropanol, 1-ethoxy- [13837-45-1], **63**, 146
 Cyclopropanol, 1-methoxy-, **63**, 151
 CYCLOPROPANONE ETHYL HEMIACETAL, **63**, 147
 Cyclopropylcarbinol [2516-33-8], **60**, 21
 CYCLOUNDECANECARBOXYLIC ACID [4373-07-3], **62**, 191
 p-Cymene, **62**, 133
 Cysteine, benzyloxycarbonyl-L-alanyl-, L-, methyl ester, **63**, 182
 Cysteine, L-, methyl ester, hydrochloride [18598-63-5], **63**, 176
 Cysteine, N-[N-[(phenylmethoxy)carbonyl]-L-alanyl]-, L-, methyl ester
 [34804-98-3], **63**, 182

 Dean-Stark trap, **62**, 125
 DECANEDIOIC ACID, DIMETHYL ESTER [106-79-6], **60**, 1
 2-DECANONE, **62**, 9
 1-Decene [872-05-9], **60**, 13; **61**, 22, 85; **62**, 9
 5-Decene, (Z)- [7433-78-5], **61**, 85
 Dehydrochlorination, of 3-acetyl-2-oxazolidinone, **62**, 149
 Dehydrochlorination, to form thiete 1,1-dioxide, **62**, 210
 DEOXYGENATION OF EPOXIDES, **60**, 29
 DIANION, OF 2-METHYLALLYL ALCOHOL, **62**, 58
 DIAZENEDICARBOXYLIC ACID, BIS(2,2,2-TRICHLOROETHYL) ESTER [38857-88-4], **61**, 17
 Diazenedicarboxylic acid, diethyl ester [1972-28-7], **62**, 57
 3H-Diazirine, 3-chloro-3-phenyl- [4460-46-2], **60**, 55
 Diazonium salts, homolytic cleavage, **62**, 70
 Diazotization, **60**, 121

2-(1,3-Dibenzoylimidazolidin-2-yl)-imidazole hydrochloride [65276-01-9],
60, **74**

2-(1,3-Dibenzoyl-4-imidazolin-2-yl)-imidazole hydrochloride [65276-00-8],
60, **74**

7,7-DIBROMO-1,6-DIMETHYLBICYCLO[4.1.0]HEPT-3-ENE [38749-43-8], **61**, **39**

1,2-Dibromoethane [106-93-4], **60**, **67**; **62**, **5**

β,β' -Dibromoisobutyric acid [41459-42-1], **61**, **77**

α,β -Dibromo- β -phenylpropionic acid, erythro- [31357-31-0], **62**, **41**

2,6-Di-*t*-butyl-4-methylpyridine [38222-83-2], **60**, **34**

recovery of, **60**, **39**

2,6-Di-*t*-butyl-4-methylpyrylium trifluoromethanesulfonate, **60**, **34**

2,6-Di-*t*-butyl-4-neopentylpyridine, **60**, **37**

Dicarboxic acid, *tert*-butyl diester, **63**, **160**

Dicarboxic acid, bis(1,1-dimethylethyl) ester [24424-99-5], **63**, **169**

Dichloroacetic acid, **62**, **24**

Dichlorobis[η^5 -cyclopentadienyl]zirconium [1291-32-3], **62**, **31**

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone [DDQ] [84-58-2], **61**, **129**

1,2-Dichloroethane, **62**, **31**

α,α -Dichloromethyl methyl ether [4885-02-3], **61**, **1**

1,1-Dichloro-2-phenylcyclopropane [2415-80-7], **60**, **6**

Dicinnamalacetone [622-21-9], **62**, **141-148**

Dicinnamalacetone, as indicator for hydrogen bromide addition, **62**, **141**

DICYCLOHEXYLCARBODIIMIDE, **63**, **183**

Dicyclopentadiene, **62**, **139**; **63**, **44**

Dicyclopentadiene, cracking, **62**, **134**

DIELS-ALDER REACTION, **61**, **147**

OF 1,2,4,5-HEXATETRAENE, **60**, **41**

Diels-Alder reaction, of 3-acetyl-2(3H)-oxazolone and 2,3-dimethyl-1,3-butadiene, **62**, 149

DIETHYL (2S,3R)-(+)-3-ALLYL-2-HYDROXYSUCCINATE, **63**, 109

Diethyl azodicarboxylate [1972-28-7], **62**, 50

Diethyl bis(hydroxymethyl)malonate [20605-01-0], **61**, 56, 77

Diethyl carbonate, **62**, 157

Diethyl chlorophosphate [814-49-3], **62**, 16, 18

Diethyl ethoxysuccinate, **60**, 59

Diethyl fumarate [623-91-6], **60**, 58, 59

DIETHYL S-(-)-MALATE, **63**, 109

Diethyl maleate, **60**, 59

Diethyl malonate [105-53-3], **60**, 67

Diethyl phosphorochloridate [814-49-3], **61**, 134; **62**, 16, 18

Diethyl succinate, **60**, 59

Diethyl tartrate [608-84-4], **61**, 24

Diethyl (2R,3R)-(+)-tartrate, **63**, 66

N-(2,4-DIFORMYL-5-HYDROXYPHENYL)ACETAMIDE [67149-23-9], **60**, 49

Diglyme [111-96-6], **61**, 103

Dihydropyran [110-87-2], **60**, 82

Diisopropylamine [108-18-9], **61**, 116; **63**, 89, 90, 203

1,4-Diketones, table, **60**, 120

Dimethoxyethane purification, **60**, 115

2,2-Dimethoxypropane, **63**, 128

2,3-DIMETHOXY-N,N,N',N'-TETRAMETHYLSUCCINIC ACID DIAMIDE, (R,R)-(+)-
[26549-29-1], **61**, 24

Dimethyl acetylenedicarboxylate [762-42-5], **60**, 43

Dimethylamine [124-40-3], **61**, 24, 116; **62**, 139

2-(N,N-Dimethylamino)phenyllithium [22608-37-3], **62**, 40
 β-[2-(N,N-DIMETHYLAMINO)PHENYL]STYRENE, (Z)- [70197-43-2], **62**, 39
 4-DIMETHYLAMINOPYRIDINE, **63**, 183
 N,N-Dimethylaniline [121-69-7], **62**, 40
 2,3-Dimethylbutadiene [513-81-5], **62**, 152
 Dimethyl carbonate, **62**, 14
 3,3-DIMETHYL-cis-BICYCLO[3.2.0]HEPTAN-2-ONE [71221-70-0], **62**, 125
 1,2-Dimethyl-1,4-cyclohexadiene [17351-28-9], **61**, 39
 DIMETHYL DECANEDIOATE [106-79-6], **60**, 1
 6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione [5617-70-9], **60**, 67
 N,N-Dimethylformamide, **62**, 40
 Dimethyl hexanedioate [627-93-0], **60**, 2
 2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID, (2SR,3RS)-, **63**, 89
 2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID, (2SR,3SR)-, **63**, 99
 2,6-Dimethylphenol, **63**, 99
 2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate, **63**, 100
 2,6-Dimethylphenyl propanoate, **63**, 99
 N,N-Dimethylphosphoramidic dichloride [677-43-0], **61**, 116
 Dimethyl 1,3-propanedioate [108-59-8], **60**, 78
 Dimethyl sulfate [77-78-1], **61**, 24
 Dimethyl tetradecanedioate, **60**, 4
 1,6-DIMETHYLTRICYCLO[4.1.0.0^{2,7}]HEPT-3-ENE, **61**, 39
 N-(2,4-Dinitrophenyl)pyridinium chloride, **62**, 134
 1,2-Diols, acetoxy bromides from, **63**, 143
 Diols, meso-, enzymic oxidation to γ-lactones, **63**, 14
 DIOLS, VICINAL, EPOXIDES FROM, **63**, 140
 m-Dioxane, 2-(2-bromoethyl)- [33884-43-4], **62**, 148

1,3-Dioxane, 2-(2-bromoethyl)- [33884-43-4], **62**, 148

1,3-Dioxane-4,6-dione, 2,2-dimethyl- [2033-24-1], **63**, 202

5,7-Dioxaspiro[2.5]octane-4,8-dione, 6,6-dimethyl- [5617-70-9], **60**, 67

1,3-Dioxolo[4,5-g]isoquinoline, 7,8-dihydro-5-phenyl- [55507-10-3], **62**, 74

Diphenylacetic acid [117-34-0], **61**, 45

Diphenyl chlorophosphate [2524-64-3], **62**, 107

1,2-DIPHENYL-3-METHYLCYCLOPROPENE [51425-87-7], **60**, 53

DIPHENYL PHOSPHORAZIDATE [26386-88-9], **62**, 187, 195

Diphenyl phosphorochloridate [2524-64-3], **62**, 187

Di-3-(+)-pinanylborane, **63**, 46

2,2'-Dipyridyl disulfide, **63**, 193

Disulfide, diphenyl [882-33-7], **63**, 192

1,3,2,4-Dithiaphosphetane, 2,4-bis(4-methoxyphenyl)-2,4-disulfide
[19172-47-5], **62**, 164

1,4-DITIASPIRO[4.11]HEXADECANE [16775-67-0], **61**, 74

1,3-Dithietane, 2,2,4,4-tetrakis(trifluoromethyl)- [791-50-4], **63**, 159

1-Docosene, **60**, 13

1,3,6,10-Dodecatetraene, 3,7,11-trimethyl- [502-61-4], **62**, 31

Dowex 50-X4 cation resin, for hydrolysis of acetals, **60**, 86

1-Eicosene [3452-07-1], **60**, 11

ELECTROHYDRODIMERIZATION, **60**, 58

 electrode assembly for, **60**, 1

Electrolysis:

 pH control in, **60**, 61

 power supply for, **60**, 60, 79

Electrophilic allyl cation synthon, **62**, 64

Elimination, of β -bromocarboxylic acids by azide ion, **62**, 39
 Enamine formation, from pyrrolidine and cyclododecanone, **62**, 191
 ENAMINES, **61**, 129
 Enamines, nitro-, reduction to indoles, **63**, 219
 ENANTIOSELECTIVE ADDITION, **61**, 42
 Enolates, alkoxy-, **63**, 114
 Enol ether, trimethylsilyl, **62**, 95
 Enol phosphate, **62**, 16
 ENZYME-CATALYZED OXIDATION OF meso-DIOLS, **63**, 10
 EPOXIDATION, **60**, 63
 EPOXIDATION, ENANTIOSELECTIVE, **63**, 66
 Epoxide ring opening, by a Grignard reagent, **62**, 48
 EPOXIDES, OPTICALLY ACTIVE, **63**, 140
 Erythorbic acid, **63**, 127
 Erythronic acid, 2,3-O-isopropylidene- γ -lactone, D-, **63**, 135
 Erythronolactone, D-, **63**, 130
 ESTERIFICATION OF CARBOXYLIC ACIDS, **63**, 183
 Esters, β -hydroxy-, stereoselective synthesis, **63**, 89, 99
 O-ESTERS, **61**, 48
 Ethanamine, N,N-diethyl- [121-44-8], **61**, 35, 77, 103; **62**, 178, 209
 Ethanaminium, N,N,N-triethyl-, salt with 4-methylbenzenesulfonic acid (1:1) [733-44-8], **63**, 213
 Ethane, 1,2-dibromo- [106-93-4], **60**, 67; **62**, 105
 Ethane, 1,1'-oxybis-, compound with trifluoroborane (1:1) [109-63-7],
61, 116; **62**, 195
 Ethane, 1,1'-oxybis(2-methoxy)- [111-96-6], **61**, 103
 1,2-Ethanediamine, N,N,N',N'-tetramethyl- [110-18-9], **61**, 141; **62**, 66

Ethanedioic acid dihydrate [6153-56-6], **60**, 21

1,2-Ethanediol [107-21-1], **61**, 65, 103

Ethanedioyl dichloride [79-37-8], **61**, 8, 134

1,2-Ethanedithiol [540-63-6], **61**, 74

1,1,2,2-ETHANETETRACARBOXYLIC ACID, TETRAETHYL ESTER, [5464-22-2], **60**, 78

Ethanimidic acid, N-(trimethylsilyl)-, trimethylsilyl ester (10416-59-8),
63, 88

Ethanol, 2-amino- [141-43-5], **62**, 157

Ethanol, thallium (1+) salt [20398-06-5], **61**, 134

Ethanone, 1-(3-nitrophenyl)- [121-89-1], **60**, 109

Ethenamine, N,N-dimethyl-2-[2-nitro-6-(phenylmethoxy)phenyl]-, (E)-
[78283-29-1], **63**, 225

Ethene [74-85-1], **62**, 124

Ethene, bromo- [593-60-2], **62**, 133

Ethene, ethoxy- [109-92-2], **63**, 88

Ether, bis(2-methoxyethyl) [111-96-6], **61**, 103

Ether, dichloromethyl methyl [4885-02-3], **61**, 1

Ether, ethyl vinyl, **63**, 80

ETHER, p-MENTH-8-EN-1-YL METHYL, cis- [24655-71-8], **61**, 112

ETHER, p-MENTH-8-EN-1-YL METHYL, trans- [24665-72-9], **61**, 112

(Ethoxycarbonylmethylene)triphenylphosphorane [1099-45-2], **62**, 203

2-[(1'-Ethoxy)-1-ethoxy]butyronitrile, **63**, 80

ETHYL ACETOACETATE, yeast reduction of, **63**, 1

Ethyl bromoacetate [105-36-2], **61**, 122; **62**, 202

ETHYL α -(BROMOETHYL)ACRYLATE [17435-72-2], **61**, 56

ETHYL 2-BUTYRYLACETATE [7152-15-0], **61**, 5

Ethyl carbamate [51-79-6], **61**, 93

ETHYL 3-CHLOROPROPANOATE, **63**, 147
 Ethyl N-chloro-N-sodiocarbamate [17510-52-0], **61**, 93
 Ethyl crotonate [623-70-1], **61**, 85
 Ethylene, **62**, 124
 Ethylene, bromo-, **62**, 133
 Ethylenediamine. N,N,N'.N'-tetramethyl- [110-18-9], **61**, 116; **62**, 66
 Ethylene dibromide [106-93-4], **60**, 67; **62**, 79
 Ethylene glycol [107-21-1], **61**, 65, 103
 Ethylene, photocycloaddition to cyclohexenone, **62**, 118
 Ethyl ether, compound with boron fluoride (BF₃) (1:1) [109-63-7],
 61, 116; **62**, 195
 ETHYL (S)-(+)-3-HYDROXYBUTANOATE, **63**, 1
 Ethyl L-(-)-lactate, **63**, 140
 Ethylmagnesium bromide, **60**, 83
 ETHYL 1-(p-METHOXYPHENYL)-2-OXOCYCLOHEXANECARBOXYLATE, **62**, 24, 25
 Ethyl 2-methylcyclohexene-1-carboxylates, **62**, 18
 Ethyl 2-oxocyclohexanecarboxylate [1655-07-0], **62**, 18, 25, 30
 ETHYL threo-[1-(2-HYDROXY-1,2-DIPHENYL)ETHYL]CARBAMATE [73197-89-4], **61**, 93
 ETHYL TRIMETHYLSILYLACETATE [4071-88-9], **61**, 122
 Ethyne [74-86-2], **62**, 8

 α-FARNESENE [502-61-4], **62**, 31
 6-Z isomer of, **62**, 35
 Flash chromatography, **62**, 77
 Flavin mononucleotide sodium salt, **63**, 12
 Fluorenone cyanohydrin, **60**, 17
 FMN, **63**, 10

FORMAMIDE ACETALS, CONDENSATION WITH, **63**, 214
 Formamide, N,N-dimethyl-, dimethyl acetal, **63**, 215
 Formic acid, **60**, 7
 Formic acid, azodi-, diethyl ester, **62**, 57
 Formic acid, chloro-, methyl ester, **60**, 83; **63**, 213
 Formic acid. chloro-. 2.2.2-trichloroethyl ester [17341-93-4], **61**, 17
 Formic acid, methyl ester [107-31-3], **61**, 1
 Formylation of phenols, **60**, 52
 3-Formylquinoline-2(1H)-thione [51925-41-8], **61**, 71
 Fumaric acid, monoethyl ester, **63**, 183
 Fumaric acid, tert-butyl ethyl ester, **63**, 184
 2-Furaldehyde [98-01-1], **62**, 178
 Furan, tetrahydro-, compound with borane (1:1) [14044-65-6], **61**, 103; **63**, 46
 2-Furancarboxaldehyde [98-01-1], **62**, 178
 2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)- [21461-84-7], **63**, 126
 2,5-Furandione [108-31-6], **61**, 147
 2,3-Furandione, dihydro-4,4-dimethyl- [13031-04-4], **63**, 25
 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-, (R)- [599-04-2], **63**, 25
 2(3H)-FURANONE, DIHYDRO-5-OCTYL- [2305-05-7], **61**, 22
 Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-, (3aR-cis)-
 [25581-41-3], **63**, 135
 2-Furoic acid, tetrahydro-5-oxo-, (S)-(-)-, **63**, 126
 Geraniol, **62**, 33
 Geranyl chloride [5389-87-7], **62**, 32
 Glutamic acid. L- [56-86-0], **63**, 121

β -HALOACETALS AND -KETALS: 2-(2-BROMOETHYL)-1,3-DIOXANE AND 2,5,5-TRIMETHYL-
 2-(2-BROMOETHYL)-1,3-DIOXANE, **62**, 140
 4-HALUBENZUOYL CHLORIDES, **61**, 8
 Halogen-lithium exchange, selective, **62**, 74
 Heneicosanoic acid, **60**, 13
 Heptadecanoic acid, **60**, 13
 1,6-Heptadien-3-ol, 4,4-dimethyl- [58144-16-4], **62**, 133
 Heptane, 1-bromo- [629-04-9], **61**, 59
 Heptanoic acid, **60**, 13
 1-Heptanoic acid, 7-(tert-butoxycarbonylamino)-, **63**, 173
 3-Heptanone, 5-hydroxy-2,4,6-trimethyl-2-[(trimethylsilyloxy)]-, (R*,S*)-(\pm)-
 [64869-24-5], **63**, 98
 6-Hepten-2-one, 4-phenyl- [69492-29-1], **62**, 86
 2-HEPTYL-2-CYCLOHEXENONE, **61**, 59
 1-Hexadecene, **60**, 13
 HEXAFLUOROACETONE, **63**, 154
 Hexafluoropropene, **63**, 154
 HEXAHYDRO-2-(1H)-AZOCINONE, **63**, 188
 2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1H-indene-
 1,5(6H)-dione, (3aS,7aS)-(+)-, **63**, 36
 Hexamethylbenzene [87-85-4], **61**, 98
 HEXAMETHYL DEWAR BENZENE [7641-77-2], **61**, 62
 Hexamethyldisiloxane, **62**, 63
 Hexamethylphosphorictriamide [680-31-9], **61**, 116
 Hexanedioic acid, dimethyl ester [627-93-0], **60**, 2
 Hexanedioic acid, monomethyl ester [627-91-8], **60**, 1
 1,4,7,10,13,16-Hexaoxacyclooctadecane [17455-13-9], **60**, 129

1,2,4,5-HEXATETRAENE [29776-96-3], **60**, 41
 1-Hexene, 1-iodo-, (Z)- [16538-47-9], **62**, 1
 Hex-2-enoic acid, D-erythro-, γ -lactone [89-65-6], **63**, 135
 2-Hexen-1-ol, (E)- [928-95-0], **63**, 66
 HOMOCONJUGATE ADDITION, **60**, 66
 HOMOLOGATION OF ACETYLENES TO ALLENES, **63**, 203
 Homo-Michael acceptor, **60**, 69
 Horse liver alcohol dehydrogenase, **63**, 10
 Hydrazine [302-01-2], **62**, 57
 Hydrazine hydrate [7803-57-8], **61**, 17; **62**, 34
 Hydrazine monohydrate [7803-57-8], **61**, 17
 Hydriodic acid [10034-85-2], **62**, 169
 HYDRIODIC ACID, REDUCTION OF QUINONE, **62**, 165
 HYDROBORATION, ASYMMETRIC, **63**, 44
 Hydrobromination, of acrolein, **62**, 140
 Hydrobromination, of methyl vinyl ketone, **62**, 140
 HYDROCINNAMALDEHYDE, α -METHYL- [5445-77-2], **61**, 82
 Hydrocinnamic acid, α,β -dibromo-, erythro-, **62**, 47
 Hydrogenation, asymmetric, **63**, 23
 Hydrogenation of nitroenamines, **63**, 219
 Hydrogen peroxide-acetonitrile, **60**, 63
 Hydrolysis, of 4-acetyl-7,8-dimethyl-2-oxa-4-azabicyclo[4.3.0]non-7-en-3-one, **62**, 149
 Hydrolysis, of a phosphoramidate, **62**, 191
 Hydroperoxide, 1,1-dimethylethyl- [75-91-2], **63**, 78
 Hydroquinone [123-31-9], **62**, 152
 Hydroquinone, inhibitor during Diels-Alder reaction, **62**, 149

17 β -HYDROXY-5 α -ANDROST-2-ENE [2639-53-4], **61**, 116
 4-Hydroxy-2-butanone [590-90-9], **60**, 93
 3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE [70702-66-8], **62**, 111
 2-Hydroxybutyronitrile, **63**, 79
 β -HYDROXYCARBOXYLIC ESTERS, α -ALKYLATION, **63**, 109
 2-Hydroxycyclobutanone [17082-63-2], **60**, 27
 5-(2-Hydroxyethyl)-4-methyl-1,3-thiazole, **62**, 178
 Hydroxylamine-O-sulfonic acid [2950-43-8], **63**, 188
 2-(HYDROXYMETHYL)ALLYLTRIMETHYLSILANE, **62**, 58
 2-HYDROXYMETHYL-2-CYCLOPENTENONE, **61**, 65
 2-Hydroxy-2-methylpentan-3-one, **63**, 81
 4-HYDROXYNONA-1,2-DIENE, **63**, 203
 5-Hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one, **63**, 89

 Imidazole, **60**, 73
 IMIDAZOLE-2-CARBOXALDEHYDE [10111-08-7], **60**, 72
 1H-IMIDAZOLE-2-CARBOXALDEHYDE [10111-08-7], **60**, 72
 Imidazolidine, 1,3-dibenzoyl-2-(1H-imidazol-2-yl)-, monohydrochloride
 [65276-01-9], **60**, 74
 Imidazolidine, 2-(1,3-diphenyl-2-imidazolidinylidene)-1,3-diphenyl-
 [2179-89-7], **60**, 50
 1,5(6H)-Indanedione, 7,7a-dihydro-7a-methyl-, (+)- **63**, 36
 1H-Indene-1,5(4H)-dione, hexahydro-3a-hydroxy-7a-methyl-, (3aS-cis)-
 [33879-04-8], **63**, 26
 1H-Indene-1,5(6H)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (S)-
 [17553-86-5], **63**, 26
 Indicator, for hydrogen bromide, **62**, 141

Indole, 4-benzyloxy-, **63**, 225
 1H-Indole, 4-(phenylmethoxy)- [20289-26-3], **63**, 225
 INDOLES FROM 2-METHYLNITROBENZENES, **63**, 214
 Indoles, polycyclic, synthesis of, **63**, 219
 Iodine [7553-56-2], **62**, 3
 1-Iodo-1-alkenes, Z-, **62**, 6
 Iodobenzene [591-50-4], **61**, 82
 1-IODOHEXENE, Z- [16538-47-9], **62**, 1
 Isoascorbic acid, D-, **63**, 130
 1,3-Isobenzofurandione [85-44-9], **60**, 101
 1(3H)-Isobenzofuranone, hexahydro-, (3aS-cis)- [65376-02-5], **63**, 17
 Isobutene [115-11-7], **61**, 116
 Isobutyraldehyde, **63**, 90
 Isobutyryl chloride [79-30-1], **61**, 5
 1-H-Isoindole-1,3(2H)-dione [85-41-6], **62**, 57
 Isopropyl alcohol, titanium(4+) salt, **63**, 78
 2,3-O-ISOPROPYLIDENE-D-ERYTHRONOLACTONE, **63**, 127
 ISOQUINOLINE, DIHYDRO, **62**, 74
 o-ISOTHIOCYANATO-(E)-CINNAMALDEHYDE [19908-01-1], **61**, 71
 o-ISOTHIOCYANATO-(Z)-CINNAMALDEHYDE [19908-02-2], **61**, 71

 α-Keto alcohols, reduction with yeast, **63**, 5
 α-Keto carboxylic acid esters, asymmetric reduction, **63**, 23
 α-Keto esters, reduction with yeast, **63**, 5
 β-Keto esters, synthesis of, **63**, 200
 α-Keto lactones, asymmetric reduction, **63**, 23
 α-Keto phosphates, reduction with yeast, **63**, 5

KETONE, CONJUGATE ALLYLATION OF α,β -UNSATURATED, **62**, 86
 KETONE, α -TERT-ALKYLATION, **62**, 95
 Ketones, α,β -acetylenic, asymmetric reduction, **63**, 63
 Ketones, cyclic, lactams from, **63**, 188
 Ketones, β -hydroxy-, synthesis of, **63**, 79
 Ketones, β -hydroxy-, α' -trimethylsilyloxy-, stereoselective synthesis of, **63**, 94
 Ketones, reduction with yeast, **63**, 5
 Ketones, α -trimethylsilyloxy-, synthesis of, **63**, 85
 KETOPANTOYL LACTONE, preparation and asymmetric hydrogenation of, **63**, 18
 Kolbe electrolysis, **60**, 4

 Lactams, synthesis of, **63**, 190
 Lactic acid, ethyl ester, L-, **63**, 146
 γ -LACTONES, CHIRAL, synthesis of, **63**, 10
 γ -Lactones, β -hydroxy-, α -alkylation, **63**, 115
 Lactonization, **63**, 124
 Lamps, photochemical, **62**, 119
 Lead tetraacetate, **62**, 24, 30
 LIMONENE [5989-27-5], **61**, 112
 Lithiation, of 2-methylallyl alcohol, **62**, 58
 Lithium [7439-93-2], **62**, 109
 Lithium aluminum hydride [16853-85-3], **61**, 42; **62**, 77
 Lithium, butyl [109-72-8], **61**, 5, 42, 74, 116; **62**, 8, 47, 66; **63**, 89, 100
 Lithium, tert-butyl-, **62**, 85
 Lithium containing 1-2% of sodium, **62**, 4
 Lithium cyanide [2408-36-8], **60**, 127

Lithium dibutylcuprate, **62**, 1, 20
 Lithium di(Z-hexenyl)cuprate, **62**, 2
 Lithium, [o-(dimethylamino)phenyl]-, **62**, 47
 Lithium, [2-(dimethylamino)phenyl]- [22608-37-3], **62**, 47
 Lithium dimethylcuprate, **62**, 16
 Lithium, (1,1-dimethylethyl) [594-19-4], **62**, 85
 Lithium hydride [7580-67-8], **60**, 127
 Lithium metal, reaction with methyl chloride, **62**, 101
 Lithium, methyl- [917-54-4], **61**, 39; **62**, 47, 101, 109
 Lithium, (1-methylpropyl)- [598-30-1], **61**, 141
 Lithium perhydro-9b-boraphenyl hydride [36005-35-3], **61**, 103
 Lithium reagents, standardization, **62**, 79

 Magnesium [7439-95-4], **60**, 42; **62**, 57
 Malic acid, diethyl ester, (S)-, **63**, 120
 Maleic anhydride [108-31-6], **61**, 147
 Malonic acid, cyclic isopropylidene ester, **63**, 202
 Malonic acid, bis(hydroxymethyl)-, diethyl ester [20605-01-0], **61**, 56, 77
 Malonic acid, monoethyl ester [1071-46-1], **61**, 5
 Malonic acid, monoethyl ester, potassium salt [6148-64-7], **61**, 5
 Manganese acetate tetrahydrate [6156-78-1], **61**, 22
 Meerwein reaction, **62**, 69
 MENSTRUUM'S ACTIO, **63**, 198
 p-MENTHA-1,8-DIENE, (+)- [5989-27-5], **61**, 112
 p-MENTH-8-EN-1-YL, cis-, METHYL ETHER [24655-71-8], **61**, 112
 p-MENTH-8-EN-1-YL, trans-, METHYL ETHER [24655-72-9], **61**, 112
 MERCAPTANS FROM THIOKETALS, **61**, 74

Mercury, (aceto-O)phenyl- [62-38-4], **61**, 82

Mercury, (aceto)phenyl- [62-38-4], **61**, 82

Mercury(II) chloride, **60**, 42

Mercury oxide [21908-53-2], **61**, 48

Mercury(II) oxide, red [21908-53-2], **61**, 48

Mercury(II) trifluoroacetate [13257-51-7], **61**, 48

Methanamine, 1,1-dimethoxy-N,N-dimethyl- [4637-24-5], **63**, 225

Methanamine, N-methyl- [124-40-3], **61**, 24, 116; **62**, 139

Methane. chloro- [74-87-3], **62**, 109

Methane, dichloromethoxy- [4885-02-3], **61**, 1

Methane, tetrachloro- [56-23-5], **61**, 35

Methane, tribromo- [75-25-2], **61**, 39

4,7-Methano-1-H-indene, 3a,4,7,7a-tetrahydro- [77-73-6], **62**, 139; **63**, 56

Methanone, diphenyl- [119-61-9], **60**, 14

p-Methoxyacetophenone cyanohydrin, **60**, 17

4-Methoxy-3-buten-2-one [4652-27-1], **61**, 147

α -Methoxycarbamates, synthesis of, **63**, 209

2-METHOXY-N-CARBOMETHOXPYRROLIDINE, **63**, 206

5 β -METHOXYCYCLOHEXAN-1-ONE-3 β ,4 β -DICARBOXYLIC ACID ANHYDRIDE, **61**, 147

p-Methoxyphenyllead, **62**, 30

p-Methoxyphenyllead triacetate, **62**, 24

trans-1-METHOXY-3-TRIMETHYLSILOXY-1,3-BUTADIENE [59414-23-2], **61**, 147

p-Methylacetophenone cyanohydrin, **60**, 17

N-Methylanilinium trifluoroacetate [29885-95-8], **60**, 88

6-METHYLBICYCLO[4.2.0]OCTAN-2-ONE [13404-66-5], **62**, 118

Methyl bromoacetate, **63**, 46

METHYL α -(BROMOMETHYL)ACRYLATE [4224-69-5], **61**, 77

(2-Methyl-1,3-butadienyl)dimethylalane, (E)-, **62**, 31, 33
 3-Methyl-3-buten-2-ol, **62**, 65
 Methyl chloride, **62**, 109
 Methyl chloride, transferring and metering, **62**, 101
 Methyl chlorocarbonate, **60**, 83; **63**, 206
 Methyl chloroformate [79-22-1], **60**, 83; **63**, 206
 2-Methyl-1,3-cyclohexanedione, **63**, 37
 2-Methyl-2-cyclohexen-1-ol, **62**, 65
 3-Methyl-2-cyclohexenone [1193-18-6], **62**, 118
 Methyl 2,4-cyclopentadiene-1-acetate, **63**, 45
 2-Methyl-1,3-cyclopentanedione, **63**, 26
 Methyl β,β' -dibromoisobutyrate [22262-60-8], **61**, 77
 Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate, **62**, 15
 4,5-METHYLENEDIOXYBENZOCYCLOBUTENE [61099-23-8], **62**, 74
 3,4-Methylenedioxyphenylacetic acid [2861-28-1], **62**, 77
 2-(3',4'-Methylenedioxyphenyl)-ethanol, **62**, 78
 α -METHYLENE KETONES AND ALDEHYDES, **60**, 88
 2-METHYLENE-1-OXO-1,2,3,4-TETRAHYDRONAPHTHALENE [13203-73-1], **60**, 88
 Methylene transfer, **60**, 90
 Methyl formate [107-31-3], **61**, 1
 Methyl hydrogen hexanedioate [627-91-8], **60**, 1
 METHYL 4-HYDROXY-2-BUTYNOATE [31555-05-2], **60**, 81
 METHYL (1R,5R)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE, **63**, 44
 METHYL KETONES FROM TERMINAL OLEFINS, **62**, 9
 Methyl lithium [917-54-4], **61**, 39; **62**, 16, 47, 109, 66
 METHYLLITHIUM, HALIDE-FREE, PREPARATION AND FILTRATION, **62**, 101
 Methyl lithium-lithium bromide complex, **62**, 19

METHYL 2-METHYL-1-CYCLOHEXENE-1-CARBOXYLATE [25662-38-3], **62**, 14
 Methyloxirane, (S)-(-)-, **63**, 141
 METHYLOXIRANES, ENANTIOMERIC, **63**, 140
 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione, **63**, 37
 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione, **63**, 26
 Methyl 2-oxocyclohexanecarboxylate [41302-34-5], **62**, 14
 2-Methyl-2-pentene [625-27-4], **61**, 85
 METHYL PHENYLACETYLACETATE, **63**, 198
 2-METHYL-3-PHENYLPROPANAL [5445-77-2], **61**, 82
 2-Methylpropane-2-thiol [75-66-1], **61**, 134
 2-Methyl-2-propen-1-ol [513-42-8], **61**, 82; **62**, 66
 1-Methylpyrrole [96-54-8], **62**, 111
 1-Methyl-2-(3H)-pyrrolethione, dihydro-, **62**, 164
 N-Methylpyrrolidinone, **62**, 164
 Methyl sulfide, compd. with borane (1:1), **63**, 139
 trans- β -Methylstyrene [873-66-5], **60**, 54
 8a-METHYL-3,4,8a-TETRAHYDRO 1,6(2H,7H) NAPHTHALENEDIONE, (S)
 [33878-99-8], **63**, 37
 N-METHYLTHIOPYRROLIDONE, **62**, 158
 2-METHYL-2-TRIMETHYLSILOXY-3-TRIMETHYLSILOXY-3-PENTANONE, **63**, 79, 90
 2-Methyl-1-trimethylsiloxy-3-trimethylsilyl-2-propene, **62**, 63
 Methyl vinyl ketone [78-94-4], **61**, 129; **62**, 148; **63**, 26, 137
 MEVALONOLACTONE-2-¹³C. (R.S)- [53771-22-5], **60**, 92
 Mitsunobu procedure, conversion of hydroxyl groups to amines, **62**, 48
 Monoethyl malonate [1071-46-1], **61**, 5
 Morpholine, 4-methyl- [109-02-4], **63**, 182

β -NAD, **63**, 10

1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-
[20007-72-1], **63**, 37

1(2H)-Naphthalenone, 3,4-dihydro- [529-34-0], **60**, 88

1(2H)-NAPHTHALENONE, 3,4-DIHYDRO-2-METHYLENE- [13203-73-1], **60**, 88

Neopentanediol [126-30-7], **62**, 141

Neryl chloride, **62**, 35

β -Nicotinamide adenine dinucleotide, **63**, 17

Nitric acid, fuming. **61**, 17

m-Nitroacetophenone, **60**, 109

p-Nitroacetophenone cyanohydrin, **60**, 17

Nitrobenzenes, indoles from, **63**, 214

m-NITROETHYLBENZENE [617-86-7], **60**, 108

Nitroolefins, **60**, 103

2-Nitro-1-propanol [2902-96-7], **60**, 102
preparation, **60**, 102

2-NITROPROPENE [4749-28-4], **60**, 101, 118

NONADECANOIC ACID [646-30-0], **60**, 11

1,2-Nonadien-4-ol [73229-28-4], **63**, 203

Nonanoic acid, **60**, 13

1,3,6,8-Nonatetraen-5-one, 1,9-diphenyl [622-21-9], **62**, 148

1-Octadecene, **60**, 13

9-Octadecenoic acid, 12-hydroxy-, [R-(E)]- [540-12-5], **63**, 197

9-Octadecenoic acid, 12-hydroxy-, [R-(Z)]- [141-22-0], **63**, 197

2,6-Octadiene, 1-chloro-3,7-dimethyl, (E)- [5389-87-7], **62**, 38

4-OCTANONE, 5-HYDROXY- [496-77-5], **62**, 170

1-Octene, **60**, 13

γ -(n-OCTYL)- γ -BUTYROLACTONE [2305-05-7], **61**, 22

1-Octyn-3-ol [818-72-4], **63**, 59, 203

1-OCTYN-3-OL, (R)-(+)- [32556-70-0], **63**, 57

1-Octyn-3-one [27593-19-7], **63**, 58

Organic peroxides:

removal, **60**, 64

test for **60**, 64

Organolithium reagents, **62**, 4

Osmium oxide [20816-12-0], **61**, 85

Osmium oxide, (T-4)- [20816-12-0], **61**, 85

Osmium tetroxide [20816-12-0], **61**, 85

6-Oxabicyclo[3.1.0]hexane [285-67-6], **62**, 57

9-OXABICYCLO[6.1.0]NONANE, cis- [4925-71-7], **60**, 63

8-OXABICYCLO[4.3.0]NONAN-7-ONE, (1R, 6S)-(+)-, **63**, 10

13-Oxabicyclo[10.1.0]tridecane, trans- [4683-60-7], **60**, 31

Oxalic acid dihydrate [6153-56-6], **60**, 21

Oxalyl chloride [79-37-8], **61**, 8, 134

1,3-OXAZEPINES, **61**, 98

2-Oxazolidinone [497-25-6], **62**, 157

2-Oxazolidinone, 3-acetyl- [1432-43-5], **62**, 157

2-Oxazolidinone, 3-acetyl-5-chloro- [60759-48-0], **62**, 157

2(3H)-Oxazolone, 3-acetyl- [60759-49-1], **62**, 149, 157

Oxazolone formation, from 2-aminoethanol and diethyl carbonate, **62**, 149

Oxetanes, in photo-addition of aldehydes to pyrrole, **62**, 115

OXIDATION OF 5-AMINOTETRAZOLES. **61**, 14

OXIDATION, ANODIC, **63**, 206

Oxidation, of 3-(hydroxyalkyl)pyrroles to 3-acylpyrroles, **62**, 115
 Oxidation, with manganese dioxide, **62**, 115
 Oxidation, of thietane to thietane 1,1-dioxide, **62**, 210
 Oxidation, of thioethers with hydrogen peroxide, **62**, 210
 Oxirane, methyl-, (S)- [116088-62-3], **63**, 146
 Oxiranes, methyl, enantiomeric, **63**, 144
 OXIRANEMETHANOL, (2S,3S)-, 3-PROPYL-, **63**, 66
 2-OXO-1-PHENYL-3-PYRROLIDINECARBOXYLIC ACID [56137-52-1], **60**, 66
 2-(2-OXOPROPYL)CYCLOHEXANONE, **60**, 17

 Palladium acetate [3375-31-3], **61**, 82
 Palladium(II) catalysis, amination of alkenes, **62**, 48
 Palladium-catalyzed cross-coupling of an alkenyl-aluminum with an allyl
 halide, **62**, 31
 PALLADIUM-CATALYZED CROSS-COUPLING, OF ORGANOLITHIUM COMPOUNDS WITH
 ALKENYL HALIDES, **62**, 39
 PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY ALLYLATION OF
 ALKENYLALANES, **62**, 31
 Palladium chloride [7647-10-1], **62**, 9, 34, 47, 57
 Palladium(II) chloride-acetonitrile. **62**, 55
 Palladium(II), oxidation of 1-alkenes, **62**, 9
 Palladium-phosphine complex reaction of organolithium compounds
 and alkenyl halides. **62**, 39
 Palladium(II), recycling with copper(II) and oxygen, **62**, 9
 Palladium, tetrakis(triphenylphosphine)- [14221-01-3], **62**, 38
 PANTOYL LACTONE, D-(-)-, **63**, 18
 Paracyclophanes, table, **60**, 47

Paraformaldehyde [30525-89-4], **61**, 65; **63**, 203
 Paraformaldehyde (polyoxymethylene), **60**, 88
 Pentadecanoic acid, **60**, 13
 2,3-Pentadienoic acid, ethyl ester, **62**, 202
 Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,S*)-(±)- [64869-26-7], **63**, 98
 Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)- [73198-99-9], **63**, 108
 Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)-, 2,6-dimethylphenyl ester, [73198-92-2], **63**, 108
 PENTANOIC-2-¹³C ACID. 3-HYDROXY-3-METHYL-5-(PHENYLMETHOXY)- [57830-65-6], **60**, 94
 PENTANOIC ACID, 4-METHYL-3-OXO-, ETHYL ESTER [7152-15-0], **61**, 5
 3-Pentanone [96-22-0], **61**, 122
 3-Pentanone, 2-hydroxy-2-methyl- [2834-17-5], **63**, 81
 3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]- [72507-50-7], **63**, 82, 90
 4-Pentenal, 2,2-dimethyl- [5497-67-6], **62**, 133
 2-Pentene, 2-methyl- [625-27-4], **61**, 85
 4-PENYLBENZOYL CHLORIDE [49/63-65-7], **61**, 8
 2-tert-PENTYLCYCLOPENTANONE [25184-25-2], **62**, 95
 Peptides, synthesis of, **63**, 178
 Perchloric acid, silver(1+) salt, monohydrate [14242-05-8], **63**, 193
 Perhydro-9b-azaphenalene [57194-67-9], **61**, 108
 PERHYDRO-9b-BORAPHENALENE [16664-33-8], **61**, 103
 Perhydrophenalene [40250-64-4], **61**, 110
 PERHYDRO-9b-PHENALENOL [16664-34-9], **61**, 103
 2-(PERHYDRO-9'b-PHENALYL)-1,3,2-DIOXABOROLE [18604-57-4], **61**, 103
 Periodic acid [10450-60-9], **63**, 91
 Phase transfer alkylation, **60**, 67

Phase transfer oxidation, **60**, 13

PHENALENE-9b(2H)-BORONIC ACID, DECAHYDRO-, CYCLIC ETHYLENE ESTER

[18604-57-4], **61**, 103

Phenylene, 9ba-chloro-2,3,3aa,4,5,6,6aa,7,8,9,9aβ,9b-dodecahydro

[33343-40-7], **61**, 109

1H-Phenylene, dodecahydro- [2935-07-1], **61**, 103

1H-Phenylene, dodecahydro-, (3aa,6aa,9aa,9bβ) [40250-64-4], **61**, 103

PHENALENE-9ba(2H)-OL, 3,3aa,4,5,6aa,7,8,9,9aβ-DECAHYDRO- [16664-34-9], **61**, 103

PHENALENE-9b(2H)-OL, DECAHYDRO-, cis,cis,trans- [16664-34-9], **61**, 103

1,10-Phenanthroline, **62**, 19

Phenol [108-95-2], **61**, 35

Phenol aldehydes, table, **60**, 51

Phenol, 2,6-dimethyl- [576-26-1], **63**, 108

Phenol, 2,6-dimethyl-, propanoate [51233-80-8], **63**, 108

Phenol, 2-methyl-3-nitro- [5460-31-1], **63**, 225

Phenols, **61**, 35

PHENYLACETYL CHLORIDE, **63**, 198

2-Phenyl-2-adamantanamine, **60**, 105

2-PHENYL-2-ADAMANTANAMINE HYDROCHLORIDE, **60**, 104

2-Phenyl-2-adamantanol [29480-18-0], **60**, 105

Phenylalanine, L- [63-91-2], **63**, 160, 171

Phenylalanine, L-, benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)- **63**, 182

PHENYLALANINE, N-tert-BUTOXYCARBONYL, L-, **63**, 171

Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-, L- [13734-34-4],

63, 169, 174

Phenylalanine, N-[N-[(phenylmethoxy)carbonyl]-L-α-aspartyl]-, L-, 4-(1,1-

dimethylethyl) ester [32771-88-3], **63**, 182

Phenylchlorodiazirine [4460-46-2], **60**, 55

PHENYL CYANATE [1122-85-6], **61**, 35

1-Phenyl-2,2-diethoxycyclopropane, **60**, 8

1-PHENYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE [55507-10-3],
62, 74, 85

Phenyl disulfide, **63**, 192

4-PHENYL-6-HEPTEN-2-ONE [69492-29-1], **62**, 86, 94

Phenylmercuric acetate [62-38-4], **61**, 82

1-PHENYL-1-PENTANOL [583-03-9], **61**, 42

1-PHENYL-1-PENTANOL, (R)-(+)- [19641-53-3], **61**, 42

1-PHENYL-1-PENTANOL, (S)-(-)- [33652-83-4], **61**, 42

N-Phenylpyrrolidinone, **60**, 68

Phosphine, triphenyl [603-35-0], **62**, 47, 57; **63**, 193

Phosphonium salt, from triphenylphosphine and ethyl bromoacetate, **62**, 202

Phosphonotrithioic acid, (p-methoxyphenyl)-bimol cyclic anhydrosulfide,
62, 164

Phosphoramidic dichloride, dimethyl- [677-43-0], **61**, 116

PHOSPHORAZIDIC ACID, DIPHENYL ESTER [26386-88-9], **62**, 187, 190, 195

Phosphoric triamide, hexamethyl- [680-31-9], **61**, 116

Phosphorochloridic acid, diethyl ester [814-49-3], **61**, 134; **62**, 23

Phosphorochloridic acid, diphenyl ester [2524-64-3], **62**, 190

Phosphorodiamidic chloride, tetramethyl- [1605-65-8], **61**, 116

Phosphorus oxide [1314-56-3], **61**, 35, 42, 116

Phosphorus oxychloride $[\text{POCl}_3]$ [10025-87-3], **61**, 116

Phosphorus pentoxide [1314-56-3], **61**, 42, 116; **62**, 19, 33

Phosphorus sulfide [12066-62-5], **62**, 164

Phosphoryl chloride [10025-87-3], **61**, 116

Photochemical apparatus, **62**, 121
 Photochlorination, of thietane 1,1-dioxide, **62**, 210
 Photocyclization of an enone to an alkene, **62**, 118
 Photocycloaddition, copper(I) catalyzed, **62**, 125
 PHOTOCYCLOADDITION, OF ETHYLENE WITH CYCLOHEXENONE, **62**, 118
 Photocycloaddition, of a 1,6-heptadiene, **62**, 125
 Photocycloadducts of enones with alkenes, table, **62**, 123
 PHOTOISOMERIZATION OF HETEROAROMATIC N-OXIDES, **61**, 98
 PHOTOPROTONATION OF CYCLOALKENES, **61**, 112
 Phthalic anhydride [85-44-9], **60**, 101
 Phthalimide [85-41-6], **62**, 50
 B-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE, **63**, 57
 2-Pinene, (1S,5S)-(-)-, **63**, 56
 2-Pinene, (1R,5R)-(+)-, **63**, 65
 Piperazine, 1-[3-(4-chlorophenyl)-1-oxo-2-propynyl]-4-methyl-
 [42122-11-2], **63**, 182
 Piperidine [110-89-4], **61**, 129
 Pivaloyl chloride [3282-30-2], **60**, 35
 Plumbane, triacetoxy(p-methoxyphenyl)- [18649-43-9], **62**, 30
 Plumbane, tris(acetyloxy)(4-methoxyphenyl)- [18649-43-9], **62**, 30
 Polyols, esterification with, **63**, 185
 Potassium cyanide [151-50-8], **62**, 201
 Potassium hydride, **62**, 15, 179
 Potassium monoethylmalonate [6148-64-7], **61**, 5
 Potassium permanganate [7722-64-7], **61**, 22
 PREPARATION OF HALIDE-FREE METHYLLITHIUM, **62**, 101
 Pressure vessel, for Diels-Alder reaction, **62**, 152

Proline, L- [147-85-3], **63**, 27, 38
 Proline, 4-hydroxy-, (-)-trans-, **63**, 33
 Proline, N-pentafluoropropionyl, L (), isopropyl ester,
 GLC analysis of, **63**, 30
 Propanal [123-38-6], **63**, 87
 Propanal, 2-methyl- [78-84-2], **63**, 98
 2-Propanamine, N-(1-methylethyl)- [108-18-9], **61**, 116; **63**, 98, 108, 203
 Propane, 2,2-dimethoxy- [77-76-9], **63**, 135
 Propanedioic acid, diethyl ester [105-53-3], **60**, 67
 Propanedioic acid, diethyl ester, ion(1-), sodium [996-82-7], **61**, 71
 Propanedioic acid, dimethyl ester [108-59-8], **60**, 78
 Propanedioic acid, monoethyl ester [1071-46-1], **61**, 5
 Propanedioic acid, monoethyl ester, potassium salt [6148-64-7], **61**, 5
 1,2-Propanediol, (S)- [4254-15-3], **63**, 146
 1,3-Propanediol [504-63-2], **62**, 148
 1,3-Propanediol, 2,2-dimethyl- [126-30-7], **62**, 148
 Propanenitrile, 2-hydroxy-2-methyl- [75-86-5], **60**, 127
 2-Propanethiol, 2-methyl- [75-66-1], **61**, 134
 2-Propanethiol, 2-methyl-, thallium(I) salt [56393-79-4], **61**, 134
 Propanoic acid, 3-bromo-2-(bromoethyl)- [41459-42-1], **61**, 77
 Propanoic acid, 3-chloro-, ethyl ester [623-71-2], **63**, 153
 Propanoic acid, 2,6-dimethylphenyl ester, **63**, 99
 Propanoic acid, 2-hydroxy-, (S)-, ethyl ester [687-47-8], **63**, 146
 Propanoic acid, 2-oxo- [127-17-3], **61**, 1
 2-Propanol, 1-bromo-, acetate, (S)- [39968-99-5], **63**, 146
 2-Propanol, 2-methyl- [75-65-0], **61**, 85, 116
 1-Propanol, 2-nitro- [2902-96-7], **60**, 102

2-Propanol, titanium(4+) salt [546-68-9], **63**, 78

2-Propanone, 1,1,1,3,3,3-hexafluoro- [684-16-2], **63**, 154

Propanoyl chloride, [79-03-8], **62**, 209; **63**, 100

Propanoyl chloride, 2,2-dimethyl- [3282-30-2], **60**, 35

Propanoyl chloride, 2-methyl [79-30-1], **61**, 5

PROPANOYL CHLORIDE, 2-OXO- [5704-66-5], **61**, 1

Propargyl alcohol [107-19-7], **60**, 82

Propargyl bromide, **60**, 42

2-Propenal. [107-02-8]. **62**. 148

2-PROPENAL, 3-(2-ISOTHIOCYANATOPHENYL)-, (E)- [19908-01-1], **61**, 71

1-Propene, 3-bromo- [106-95-6], **62**, 57; **63**, 120

1-Propene, 3,3-diethoxy-2-phenyl-, **60**, 7

1-Propene, 1,1,2,3,3,3-hexafluoro- [116-15-4], **63**, 159

1-Propene, 2-methyl- [115-11-7], **61**, 116

2-PROPENENITRILE, 3-PHENYL-, (E)- [1885-38-7], **62**, 186

1-PROPENE, 2-NITRO- [4789-28-4], **60**, 101, 118

2-PROPENOIC ACID, 2-(BROMOMETHYL)-, ETHYL ESTER [17435-72-2], **61**, 56

2-PROPENOIC ACID, 2-(BROMOETHYL)-, METHYL ESTER [4224-69-5], **61**, 77

2-Propenoic acid, 3-phenyl-, (E)- [140-10-3], **62**, 47

2-Propen-1-ol, 2-methyl- [513-42-8], **61**, 82; **62**, 66

2-Propen-1-ol, 2-[(trimethylsilyl)methyl]-, acetate [72047-94-0], **62**, 66

trans-2-(2-Propenyl)cyclopentanol [74743-89-8], **62**, 49

cis-2-(2-Propenyl)cyclopentylamine [81097-02-1], **62**, 50

Propionaldehyde, **63**, 79

Propionic acid, 3-bromo-2-(bromomethyl)-, methyl ester [22262-60-8], **61**, 77

Propionic acid, 3-chloro-, ethyl ester, **63**, 153

Propionyl chloride, **62**, 209; **63**, 108

1-Propyne, 3-bromo- [106-96-7], **60**, 42

2-Propyn-1-ol [107-19-7], **60**, 82

2-Propyn-1-one, 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-, **63**, 175

2H-Pyran, 3,4-dihydro- [110-87-2], **60**, 82

2H-Pyran, tetrahydro-2-(2-propynyloxy)- [6089-04-9], **60**, 82

2H-Pyran-2-one-3-¹³C, tetrahydro-4-hydroxy-4-methyl- [53771-22-5], **60**, 92

4-Pyridinamine, N,N-dimethyl- [1122-58-3], **63**, 187

Pyridine, **62**, 25, 78

PYRIDINE, 2,6-BIS(1,1-DIMETHYLETHYL)-3-METHYL- [38222-83-2], **60**, 34

Pyridine, 2,2'-dithiobis- [2127-03-9], **63**, 197

Pyridine, nucleophilic addition to 4-chloro-1,3-dinitrobenzene, **62**, 134

Pyridinium, 3-carbamoyl-1-β-D-ribofuranosyl hydroxide, 5' + 5' - ester with adenosine 5'-(trihydrogen pyrophosphate), inner salt, **63**, 17

Pyrido(2,1,6-de)quinolizine, dodecahydro-, cis,cis-: (3α,6α,9α) [57147-56-6]; cis,trans-: (3α,6α,9αβ) [57194-67-9], **61**, 108

Pyrrole, 3-acyl, **62**, 115

Pyrrole, 3-(1-hydroxyalkyl), **62**, 115

1H-Pyrrole-3-methanol, 1-methyl-α-propyl- [70702-66-8], **62**, 111, 117

Pyrrole, 1-methyl- [96-54-8], **62**, 117

1H-Pyrrole, 1-methyl- [96-54-8], **62**, 117

Pyrrole, photochemical addition of butyraldehyde, **62**, 111

Pyrrolidine [123-75-1], **62**, 195; **63**, 205, 215

1-Pyrrolidinecarboxylic acid, methyl ester [56475-80-0], **63**, 213

1-Pyrrolidinecarboxylic acid, 4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-, (2S-cis)-, 1,1-dimethylethyl ester [61478-28-2], **63**, 25

1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester [56475-88-8], **63**, 206

PYRROLIDINECARBOXYLIC ACID, 2-OXO-1-PHENYL- [56137-52-1], **60**, 66

2-Pyrrolidinethione, 1-methyl [10441-57-3], **62**, 158-164

2-Pyrrolidinone, 1-methyl- [872-50-4], **62**, 164

Pyruvic acid [127-17-3], **61**, 1

PYRUVOYL CHLORIDE [5704-66-5], **61**, 1

Quinoline [91-22-5], **61**, 71

3-Quinolinecarboxaldehyde, 1,2-dihydro-2-thioxo- [51925-41-8], **61**, 71

Quinoline 1-oxide [1613-37-2], **61**, 98

Quinoline N-oxide [1613-37-2], **61**, 98

2(1H)-Quinolinone [59-31-4], **61**, 98

QUINONES, REDUCTION TO HYDROCARBONS WITH HYDRIODIC ACID, **62**, 165

Radical addition, to electron-deficient double bonds, **62**, 69

Radicals, aryl, **62**, 67

Red phosphorus, **62**, 165

Reduction, amino acids to amino alcohols, **63**, 138

Reduction, asymmetric, of acetylenic ketones, **63**, 62

Reduction, asymmetric, of lactones, **63**, 23

Reduction, enantioselective, **63**, 4

REDUCTION OF KETONES, **60**, 108

Reduction of nitroenamines, **63**, 219

Reduction, of quinones to hydrocarbons with hydriodic acid, **62**, 165

REDUCTION OF QUINONES WITH HYDRIODIC ACID: BENZ[a]ANTHRACENE, **62**, 165

Reduction, with yeast, of ethyl acetoacetate, **63**, 1

REDUCTIVE ALKYLATION, **61**, 59

Reductive arylation of electron-deficient olefins, **62**, 67

REDUCTIVE CLEAVAGE OF VINYL PHOSPHATES, **61**, 116

REDUCTIVE COUPLING, **60**, 113

table, **60**, 116

Regioselectivity, in addition of aryl radicals to electron-deficient alkenes, **62**, 67

Retinol, esterification of, **63**, 185

Rhodium, di- μ -chlorobis[(1,2,5,6- μ)-1,5-cyclooctadiene] di-[12092-47-6], **63**, 25

Riboflavine 5'-(dihydrogen phosphate), monosodium salt [130-40-5], **63**, 17

Ribofuranosylpyridinium, 1- β -D-, hydroxide, inner salt [53-84-9], **63**, 17

Ricinelaiddic acid, **63**, 192

Ricinelaiddic acid lactone, **63**, 193

RICINOLEIC ACID LACTONE, **63**, 192

Ricinolic acid, **63**, 192

Ring contraction, of 1-(n-pyrrolidino)-1-cyclododecene, **62**, 191

Silane, allyltrimethyl, **62**, 94

Silanecarbonitrile, trimethyl- [7677-24-9], **60**, 15, 126; **62**, 201

Silane, chlorotrimethyl- [75-77-4], **60**, 127; **61**, 122, 147;

62, **66**, 100, 201; **63**, 147

Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl] [17082-61-0], **60**, 19

Silane, (1-cyclopenten-1-yloxy)trimethyl- [19980-43-9], **62**, 100

Silane, (1-cyclohexen-1-yloxy)trimethyl- [6651-36-1], **60**, 110

Silane, [(1-ethoxycyclopropyl)oxy]trimethyl- [27374-25-0], **63**, 153

SILANE, [(1-ETHYL-1-PROPENYL)OXY]TRIMETHYL-, (Z)- [51425-54-8], **61**, 122

SILANE, [(3 METHOXY 1 METHYLENE 2 PROPENYL)OXY]TRIMETHYL

[59414-23-1], **61**, 147

Silane, triethyl- [617-86-7], **60**, 109
 Silane, trimethyl-2-propenyl- [762-72-1], **62**, 94
 Silver oxide, **60**, 95
 Silver perchlorate, **63**, 193
 SILYLATION OF KETONES, **61**, 122
 Silylation of 2-methyl-2-propen-1-ol dianion, **62**, 58
 Silylation, of organo-lithium compounds, **62**, 58
 Silyl enol ethers, **60**, 117
 Silyl enol ether, of cyclopentanone, **62**, 95
 Sodio diethyl malonate [996-82-7], **61**, 71
 Sodium azide [26628-22-8], **62**, 47, 190
 Sodium benzophenone radical anion, **62**, 79
 Sodium borohydride [16940-66-2], **61**, 85
 Sodium cyanide [143-33-9], **61**, 35
 Sodium cyclopentadienide, **62**, 134
 Sodium hydride, **62**, 15
 Sodium hypobromite, **61**, 14
 Sodium ketyl of benzophenone, **62**, 17
 Sodium methoxide, **62**, 134
 Sodium methoxide, anhydrous, **62**, 142
 Sodium nitrite, **62**, 69
 Spiroacylals, **60**, 69
 SPIRO[5,7]TRIDECA-1,4-DIEN-3-ONE [41138-71-0], **61**, 129
 SPIRO[5,7]TRIDEC-1-EN-3-ONE [60033-39-8], **61**, 129
 Steam distillation, **62**, 179
 Stetter procedure. for the acyloin condensation. **62**, 170
 Stilbene, (E)- [103-30-0], **61**, 93

Styrene, **60**, 7, 13

α -formylation of, **60**, 10

Styrene, 6-benzyloxy- β -dimethylamino-2-nitro-, (E)-, **63**, 215

Styrene, 6-benzyloxy-2-nitro- β -pyrrolidino, (E)-, **63**, 215

Styrene, β -bromo-, (Z)-, **62**, 47

SUCCINAMIDE, 2,3-DIMETHOXY-N,N,N',N'-TETRAMETHYL-, (+)- [26549-29-1], **61**, 24

Sulfonamides, formation from the amine, **62**, 48

Sulfuric acid, dimethyl ester [77-78-1], **61**, 24

SYNTHESIS AND DIELS-ALDER REACTIONS OF 3-ACETYL-2(3H)-OXAZOLONE, **62**, 149

SYNTHESIS OF AZULENE, **62**, 134

SYNTHESIS OF α,β -UNSATURATED NITRILES FROM ACETONITRILE, **62**, 179

Tartaric acid, (R,R)-(+)- [87-69-4], **61**, 24

Tartaric acid, (S,S)-(-)- [147-71-7], **61**, 24

Tartaric acid, (R,R)-(+)-, diethyl ester [608-84-4], **61**, 24; **63**, 78

TARTRAMIDE, N,N,N',N'-TETRAMETHYL-, (+)- [26549-65-5], **61**, 24

Tetrabutylammonium fluoride hydrate [22206-57-1], **61**, 122

Tetrabutylammonium hydroxide [2052-49-5], **61**, 122

Tetrabutylammonium perchlorate [1923-70-2], **60**, 58

1-Tetradecene, **60**, 13

Tetraethylammonium p-toluenesulfonate, **63**, 207

TETRAETHYL 1,2,3,4-BUTANETETRACARBOXYLATE [4373-15-3], **60**, 58

2,3,7,7a-TETRAHYDRO-7a-METHYL-1H-INDENE-1,5-(6H)-DIONE, (7aS)-(+)-, **63**, 26

Tetrahydro-2-(2-propynyloxy)-2H-pyran [6089-04-9], **60**, 82

Tetrakis(triphenylphosphine)palladium, **62**, 32

α -Tetralone [529-34-0], **60**, 88

N,N,N',N'-Tetramethyldiamidophosphorochloridate [1605-65-8], **61**, 116
 N,N,N',N'-TETRAMETHYL-1,4-DIAMINO-2,3-DIMETHOXYBUTANE, (S,S)-(+)-, [DDB]
 [26649-21-3], **61**, 24, 42
 N,N,N',N'-Tetramethyl-1,7-diaza-1,3,5-heptatriene, in the preparation
 of azulene, **62**, 134
 TETRAMETHYL 1,1,2,2-ETHANETETRACARBOXYLATE [5464-22-2], **60**, 78
 Tetramethylethylenediamine [110-18-9], **61**, 116, 141; **62**, 66
 in lithiation of 2-methylallyl alcohol, **62**, 58
 TETRAMETHYL [2.2]PARACYCLOPHANE-4.5.12.13-TETRACARBOXYLATE. **60**, 41
 N,N,N',N'-TETRAMETHYLTARTARIC ACID DIAMIDE, (R,R)-(+)- [26549-65-5], **61**, 24
 1,1',3,3'-Tetraphenyl-2,2'-bifimidazolidinyldiene [2179-89-7], **60**, 50
 1H-Tetrazol-5-amine [4418-61-5], **61**, 14
 1H-TETRAZOL-5-AMINE, N-(PHENYLMETHYL)- [14832-58-7], **61**, 14
 1H-Tetrazole, 5-amino [4418-61-5], **61**, 14
 1H-Tetrazole, 5-amino-, monohydrate [15454-54-3], **61**, 14
 1H-TETRAZOLE, 5-(BENZYLAMINO)- [14832-58-7], **61**, 14
 Thallium(I) ethoxide [20398-06-5], **61**, 134
 Thallium(I) 2-methylpropane-2-thiolate [56393-79-4], **61**, 134
 Thiacyclobutene, derivatives, **62**, 210
 THIATION, OF N-METHYLPYRROLIDONE, **62**, 158
 THIATION WITH 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE
 2,4-DISULFIDE, **62**, 158
 5-Thiazoleethanol, 4-methyl- [137-00-8], **62**, 178
 Thiazolium, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-, chloride, **62**, 178
 Thiazolium, 5-(2-hydroxyethyl)-4-methyl-3-(phenylmethyl)-, chloride
 [4568-71-2], **62**, 178
 Thiazolium ion, catalysis of the acyloin condensation, **62**, 170

Thietane [287-27-4], **62**, 217
 Thietane, 3-chloro-, 1,1-dioxide [15953-83-0], **62**, 217
 Thietane 1,1-dioxide [5687-92-3], **62**, 217
 Thiete 1,1-dioxide, **62**, 217
 2H-Thiete 1,1-dioxide [7285-32-7], **62**, 217
 THIETE 1,1-DIOXIDE AND 3-CHLOROTHIETE 1,1-DIOXIDE, **62**, 210
 2H-Thiete 1,1-dioxide and 2H-thiete, 3-chloro-, 1,1-dioxide, **62**, 210
 Thiocarbonyl group, formation from carbonyl, **62**, 158
 Thioesterification, of carboxylic acids, **63**, 185
 THIOL ESTERS, **61**, 48
 preparation of, **61**, 134
 Thionyl chloride [7719-09-7], **62**, 78, 85
 Thiophosgene [463-71-8], **61**, 71
 Titanium metal, **62**, 67
 Titanium(IV) isopropoxide, **63**, 66
 Titanium(III) sulfate, **62**, 68
 Titanium tetrachloride [7550-45-0], **62**, 94, 100
 Titanium tetrachloride, catalysis of α -tert-alkylation of
 ketones, **62**, 95
 Titanium tetrachloride, catalysis of conjugate addition of
 allyltrialkylsilanes, **62**, 86
 Titanium trichloride [7705-07-9], **60**, 113; **62**, 73
 Toluene, 6-benzyloxy-2-nitro-, **63**, 214
 Toluene, α -chloro-, **62**, 178; **63**, 225
 p-Toluenesulfonamide, N-chloro-, sodium salt [7080-50-4], **61**, 85
 cis-2-(p-TOLUENESULFONAMIDO)CYCLOHEXANOL [58107-40-7], **61**, 85
 p-Toluenesulfonic acid, hydrate, **62**, 141

p-Toluenesulfonic acid, tetraethylammonium salt, **63**, 213

p-Toluenesulfonyl chloride, **62**, 57

Tosylated enamines. **62**, 55

N-TOSYL-3-METHYL-2-AZABICYCLO[3.3.0]OCT-3-ENE, cis- [81097-07-6], **62**, 48

1-N-Tosyl-2-(2-propenyl)cyclopentylamine, cis-, **62**, 51

Tributylamine, **62**, 62

2,2,2-TRICHLOROETHYL CHLOROFORMATE [17341-93-4], **61**, 17

Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl-, **60**, 105

TRICYCLO[3.3.1.1^{3,7}]DECAN-2-AMINE, 2-PHENYL-, HYDROCHLORIDE, **60**, 104

Tricyclo[3.3.1.1^{3,7}]decane, 2-azido-2-phenyl- [65218-96-4], **60**, 104

TRICYCLO[3.3.1.1^{3,7}]DECANE, TRICYCLO[3.3.1.1^{3,7}]DECYLIDENE-
[30541-56-1], **60**, 113

Tricyclo[3.3.1.1^{3,7}]decan-2-ol, 2-phenyl- [29480-18-0], **60**, 105

Tricyclo[3.3.1.1^{3,7}]decanone [700-58-3], **60**, 105, 113

TRICYCLO[8.2.2.2^{4,7}]HEXADECA-4,6,10,12,13,15-HEXAENE-5,6,11,12-
TETRACARBOXYLIC ACID, TETRAMETHYL ESTER [37437-90-4], **60**, 41

Tridecanoic acid, **60**, 13

Triethylamine [121-44-8], **61**, 35, 77, 103; **62**, 95, 178, 209

Triethylbenzylammonium chloride [56-37-1], **60**, 7, 68; **61**, 24, 85

Triethylsilane [617-86-7], **60**, 109

m-TRIFLUOROMETHYLBENZENESULFONYL CHLORIDE [777-44-6], **60**, 121

2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane, **63**, 154

α,α,α -Trifluoro-m-toluidine [98-16-8], **60**, 121

2,4,6-Trisopropylbenzenesulfonylhydrazide [39085-59-1], **61**, 141

Trimethylalane, **62**, 31

Trimethylamine, 1,1-dimethoxy-, **63**, 225

Trimethylchlorosilane [75-77-4], **60**, 127; **61**, 122, 147;
62, 66, 100, 201; **63**, 147

3,7,11-Trimethyl-1,3,6,10-dodecatetraene, (3E,6E)- [502-61-4], **62**, 32

Trimethylenemethane-palladium complex, **62**, 65

Trimethylene sulfide, **62**, 217

3-TRIMETHYLSILOXY-2-PENTENE, (Z)- [51425-54-8], **61**, 122

N,O-Bis(trimethylsilyl)acetamide, **63**, 82

O-(Trimethylsilyl)benzophenone cyanohydrin [40326-25-8], **60**, 15

TRIMETHYLSILYL CYANIDE [7677-24-9], **60**, 15, 126; **62**, 201

O-Trimethylsilyl-4-methoxymandelonitrile, **62**, 201

1-Trimethylsilyloxycyclohexene [6651-36-1], **60**, 118

1-Trimethylsilyloxycyclopentane, **62**, 100

Triphenylphosphine, **62**, 33, 47, 57, 202; **63**, 193

Tryptophan, 5-bromo-N-tert-butoxycarbonyl-, DL-, **63**, 173

Tryptophan, N-tert-butoxycarbonyl-5-fluoro-, DL-, **63**, 173

Tryptophan, N-tert-butoxycarbonyl-6-fluoro-, DL-, **63**, 173

Tryptophan, N-tert-butoxycarbonyl-5-methoxy-, DL-, **63**, 173

Tryptophan, N-tert-butoxycarbonyl-1-methyl-, DL-, **63**, 173

Tryptophan, N-tert-butoxycarbonyl-5-methyl-, DL-, **63**, 173

Tungsten chloride [13283-01-7], **60**, 30

Tungsten hexachloride [13283-01-7], **60**, 30

Tungstic acid [7783-03-1], **62**, 217

Tyrosine, tert-butoxycarbonyl-, DL-, **63**, 173

Valine, L- [72-18-4], **63**, 136

Valine, benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-, L-,
 methyl ester, **63**, 176

Valine, L-, methyl ester, hydrochloride [6306-52-1], **63**, 182

Valine, N-[N-[N-[(phenylmethoxy)carbonyl]-L- α -aspartyl]-L-phenylalanyl]-, L-,
4-(1,1-dimethylethyl) 1-methyl ester [57850-41-6], **63**, 182

VALINOL, L-, **63**, 136

VICINAL OXYAMINATION OF OLEFINS, **61**, 85, 93

Vinyl cuprate, **62**, 3

Vinyllic cuprates, (Z)-, **62**, 7

VINYLLITHIUM REAGENTS, GENERATION AND REACTIONS OF, **61**, 141

Vinylmagnesium bromide, addition to aldehyde, **62**, 125

Vitamin A, esterification of, **63**, 185

Wacker oxidation of 1-alkenes, **62**, 9

Wittig reagent, addition to acid chlorides, **62**, 202

Wolff-Kishner reaction, **60**, 111

YEAST REDUCTION, of ethyl acetoacetate, **63**, 1

Zinc [7440-66-6], **61**, 122

Zinc cyanide [557-21-1], **62**, 201

Zinc cyanide, as catalyst in cyanohydrin formation, **62**, 196

Zirconium-catalyzed carboalumination of alkynes, **62**, 31

Zirconium, dichloro- π -cyclopentadienyl-, **62**, 38

Zirconium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- [1291-32-3],
62, 38

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CONTENTS

Rammath S. Iyer and Paul Helquist	1	ADDITION OF AN ETHYLCOPPER COMPLEX TO 1-OCTYNE: (E)-5-ETHYL-1,4-UNDECADIENE
P. A. Wender, D. A. Holt, and S. McN. Sieburth	10	2-ALKENYL CARBINOLS FROM 2-HALO KETONES: 2-E-PROPENYLCYCLOHEXANOL
John L. LaMattina and R. T. Suleske	19	α -AMINO ACETALS: 2,2-DIETHOXY-2-(4-PYRIDYL)ETHYLAMINE
Steven H. Bertz, James M. Cook, Ali Gawish, and Ulrich Weiss	27	CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH 1,2-DICARBONYL COMPOUNDS: <i>cis</i> -BICYCLO[3.3.0]OCTANE-3,7-DIONES
Paul G. Gassman and Thomas L. Guggenheim	39	CONVERSION OF EPOXIDES TO β -HYDROXY ISOCYANIDES. TRANS-2-ISOCYANOCYCLOHEXANOL
Ei-ichi Negishi, Anthony O. King, and James M. Tour	44	CONVERSION OF METHYL KETONES INTO TERMINAL ALKYNES. (E)-BUTEN-3-YNYL-2,6,6-TRIMETHYL-1-CYCLOHEXENE
J. Salaün and A. Fadel	50	CYCLOBUTENE
S. Iacono and James R. Rasmussen	57	DEOXYGENATION OF SECONDARY ALCOHOLS: 3-DEOXY-1,2:5,6-DI-O-ISOPROPYLIDENE- α -D-ribo-HEXOFURANOSE
Paloma Ballesteros and Bryan W. Roberts	63	DI- <i>tert</i> -BUTYL METHYLENEMALONATE
Andrew S. Kende and Pawel Fludzinski	68	THE STORK-DANHEISER KINETIC ALKYLATION PROCEDURE. SYNTHESIS OF 3-ETHOXY-6-METHYL-2-CYCLOHEXEN-1-ONE
Andrew S. Kende and Pawel Fludzinski	73	DICHLOROVINYLACTION OF AN ENOLATE. SYNTHESIS OF 8-ETHYNYL-8-METHYL-1,4-DIOXASPIRO[4.5]DEC-6-ENE
Arthur F. Kluge	80	DIETHYL [(2-TETRAHYDROPYRANYLOXY)-METHYL]PHOSPHONATE
John T. Gupton and Steven A. Andrews	85	β -DIMETHYLAMINOMETHYLENATION: N,N-DIMETHYL-N'-p-TOLYLFORMAMIDINE
Brian L. Benac, Edward M. Burgess, and Anthony J. Arduengo, III	92	1,3-DIMETHYLIMIDAZOLE-2-THIONE

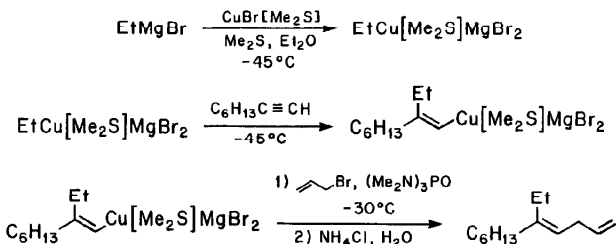
W. Klötzer, J. Stadlwieser, and J. Raneburger	96	ELECTROPHILIC N-AMINATION OF IMIDE SODIUM SALTS WITH O-DIPHENYLPHOS- PHINYLHYDROXYLAMINE (DPH): 7- AMINO THEOPHYLLINE
Andrew S. Kende and Paweł Fludzinski	104	ETHYL 4-HYDROXYCROTONATE
Michael J. Taschner, Terry Rosen and Clayton H. Heathcock	108	ETHYL ISOCROTONATE
George A. Olah and Massoud Arvanaghi	114	FORMYL TRANSFER TO GRIGNARD REAGENTS: 3-PHENYLPROPIONALDEHYDE
George M. Rubottom, John M. Gruber, Henrik D. Juve, Jr., and Dan A. Charleson	118	α -HYDROXY KETONES FROM THE OXIDATION OF ENOL SILYL ETHERS WITH m-CHLOROPERBENZOIC ACID: 6- HYDROXY-3,5,5-TRIMETHYL-2- CYCLOHEXEN-1-ONE
Edwin Vedejs and S. Larsen	127	HYDROXYLATION OF ENOLATES WITH OXODIPEROXYMOLYBDENUM(PYRIDINE)- (HEXAMETHYLPHOSPHORIC TRIAMIDE), MoO ₅ ·Py·HMPA (MoOPH): 1,7,7-TRIMETHYL-3-HYDROXY- BICYCLO[2.2.1]HEPTAN-2-ONE
Robert M. Moriarty, Kwang-Chung Hou, Indra Prakash, and S. K. Arora	138	α -HYDROXYLATION OF A KETONE USING o-IODOSYLBENZOIC ACID: α -HYDROXYACETOPHENONE VIA THE α -HYDROXY DIMETHYLACETAL
C. R. Hutchinson, M. Nakane, H. Gollman, and P. L. Knutson	144	METHYL DIFORMYLACETATE
Ronald E. Claus and Stuart L. Schreiber	150	OZONOLYTIC CLEAVAGE OF CYCLOHEXENE TO TERMINALLY DIFFERENTIATED PRODUCTS: METHYL 6-OXOHXANOATE, 6,6-DIMETHOXYHEXANAL, METHYL 6,6-DIMETHOXYHXANOATE
Leo A. Paquette and Richard V. C. Carr	157	PHENYL VINYL SULFONE AND SULFOXIDE
Eric J. Leopold	164	SELECTIVE HYDROBORATION OF A 1,3,7-TRIENE: HOMOGERRANOL
F. Bermejo González and Paul A. Bartlett	175	STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC ACIDS: THE TRANS AND CIS ISOMERS OF 4,5- DIHYDRO-5-IODOMETHYL-4-PHENYL- 2(3H)-FURANONE

Todd K. Jones and Scott E. Denmark	182	STEREOSPECIFIC REDUCTION OF PROPARGYL ALCOHOLS: (E)-3- TRIMETHYLSILYL-2-PROPEN-1-OL
Kevin T. Potts, Philip Ralli, George Theodoridis, and Paul Winslow	189	2,2':6',2"-TERPYRIDINE
Martin Hulce, John P. Mallamo, Leah L. Frye, Timothy P. Kogan, and Gary H. Posner	196	(S)-(+)-2-(p-TOLUENESULFINYL)- 2-CYCLOPENTENONE: PRECURSOR FOR ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED CYCLOPENTANONES
Xavier Creary	207	TOSYLHYDRAZONE SALT PYROLYSES: PHENYLDIAZOMETHANES
Stephen L. Taylor, T. R. Forbus, Jr., and J. C. Martin	217	TRIFLUOROACETYL TRIFLATE
William J. Middleton	221	TRIS(DIMETHYLAMINO)SULFONIUM DIFLUOROTRIMETHYLSILICATE
Unchecked Procedures	226	
Cumulative Author Index for Volumes 60, 61, 62, 63, and 64	231	
Cumulative Subject Index for Volumes 60, 61, 62, 63, and 64	235	

ADDITION OF AN ETHYLCOPPER COMPLEX TO 1-OCTYNE:

(E)-5-ETHYL-1,4-UNDECADIENE

(1,4-Undecadiene, 5-ethyl-, (E)-)



Submitted by Ramnath S. Iyer and Paul Helquist.¹

Checked by Brian H. Johnston and Andrew S. Kende.

1. Procedure

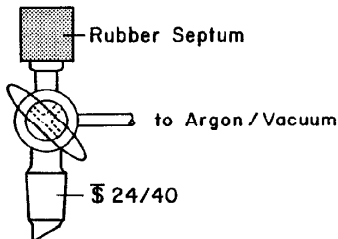
Caution! This experiment should be performed in an efficient fume hood because of the unpleasant odor of dimethyl sulfide.

A dry, 1-L, one-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock bearing a rubber septum (Note 1), and the flask is charged with 25.2 g (0.123 mol) of the dimethyl sulfide complex of cuprous bromide (Note 2). An argon or nitrogen (Note 3) atmosphere is established in the flask by repeated cycles of evacuation with an oil pump and refilling with the inert gas. Through use of a syringe or cannula, 150 mL of diethyl ether (Note 4) and 120 mL of dimethyl sulfide

(Note 4) are added. After the mixture is stirred for a few minutes at 25°C, the resulting clear and colorless solution is cooled to -45°C (Notes 5,6). A 2.73 M solution (45.0 mL, 0.123 mol) of ethylmagnesium bromide in ether (Note 7) is added dropwise with a syringe or cannula over a period of 10 min. The suspension of yellow-orange solid is stirred at -45°C for 2 hr, and 1-octyne (16.0 mL, 0.109 mol; Note 4) is added with a syringe or cannula over a period of 2 min. After the solution is stirred at -45°C for 2 hr, it is cooled to -78°C (Note 5) and maintained at this temperature during the successive additions of hexamethylphosphoric triamide (40 mL, 0.229 mol; Note 4) (Caution: *Hexamethylphosphoric triamide is a potent carcinogen. Avoid inhalation of vapor, ingestion of the liquid, and contact with skin.*) and allyl bromide (11.4 mL, 0.131 mol; Note 4). The mixture is immediately warmed to -30°C and stirred at -30°C for 12 hr; it is warmed to 0°C and quenched by the addition of 30 mL of a saturated, aqueous solution of ammonium chloride adjusted to pH 8 with ammonium hydroxide. The mixture is stirred at 25°C in the air for 1.5 hr (Note 8) and is then shaken in a separatory funnel with a mixture of additional diethyl ether (50 mL) and water (50 mL). The dark blue aqueous layer is drawn off and the organic layer is washed with additional 50-mL portions of the ammonium chloride solution (pH 8) until the washings are colorless. The organic layer is washed separately with water (50 mL) and saturated aqueous sodium chloride solution (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation at 25°C (25 min). The residue consists of 17.6 g of yellow oil which is purified by distillation under reduced pressure through a 15-cm Vigreux column to give 16.6 g (85%) of (E)-5-ethyl-1,4-undecadiene as a clear, colorless liquid, bp 56°C (0.70 mm; Note 9).

2. Notes

1. The stopcock is constructed as shown below so that a source of inert gas and vacuum may be attached to the horizontal tubulation and liquid reagents and solutions may be transferred into the reaction flask with a syringe needle or cannula inserted through a rubber septum placed over the end of the vertical tubulation. In order to avoid air leaks through the septum into the reaction flask when reagents are not being added, the stopcock is normally turned to close off the vertical tubulation, but to leave the flask open to the argon source.



2. This complex is prepared from cuprous bromide and dimethyl sulfide according to the procedure of House.² The complex must be pure white. Slightly impure samples will produce pinkish solutions which are unsatisfactory for this procedure. Normally, the complex is dark red when it is first prepared, but the required state of purity can be achieved by two or three recrystallizations under a nitrogen atmosphere as described by House.² We have found, however, that if the initially-formed complex has a distinctly green appearance, it cannot be purified satisfactorily. Others have also been concerned about this matter of purification.³

3. The checkers found that the yields were diminished if the reaction was run under prepurified nitrogen, but did obtain the reported yields using argon. The submitters, however, have never experienced difficulty using the prepurified nitrogen available in their laboratory.

4. Commercially-obtained materials were purified before use as described below. Diethyl ether was distilled from a dark blue or dark purple solution of sodium benzophenone radical anion or dianion under nitrogen. This solution was obtained by dissolving 10 g of benzophenone in 1 L of commercial anhydrous ether, adding 10 g of freshly pressed sodium wire, and heating the mixture at reflux under nitrogen until the characteristic blue or purple color developed. Dimethyl sulfide (Aldrich Chemical Company, Inc.), 1-octyne (Chemical Samples Company or Albany International Chemicals), and allyl bromide (Columbia Organics) were distilled under nitrogen at atmospheric pressure. Hexamethylphosphoric triamide (Aldrich Chemical Company, Inc.) was distilled at aspirator pressure from calcium hydride.

5. Constant temperatures were maintained by using dry ice-acetone (-78°C) or dry ice-acetone-carbon tetrachloride baths (-25° to -45°C ; the temperature tends toward the upper part of this range as the amount of acetone used is decreased) or more conveniently through the use of an acetone bath equipped with a Neslab CryoCool Model CC-100F low temperature unit, a Cole-Parmer Versa-Therm Model 2158 temperature controller, and a 500-W immersible heating coil. The temperature of the alkenylcopper solution must not be allowed to exceed -15°C ; above this temperature rapid coupling to give a diene occurs.

6. When the solution of the cuprous bromide complex is cooled, a portion of the reagent may precipitate, but this behavior does not affect the overall results of the experiment.

7. The ethylmagnesium bromide solution was obtained from Alfa Products, Morton Thiokol, Inc. and was titrated before use by the method of Watson and Eastham.⁴

8. Stirring the mixture in the air simplifies the workup procedure because cuprous complexes are oxidized to cupric compounds that are highly soluble in water or the aqueous ammonia workup medium of this experiment.

9. The spectral characteristics of the final product are as follows: IR (neat) cm^{-1} : 3080, 2960, 2915, 2800, 1660, 1640, 1465, 1175, 940, and 910; H^1 NMR (80 MHz, CDCl_3) δ : 5.50-6.05 (m, 1 H, alkenyl C-H), 4.70-5.20 (m, 3 H, other alkenyl C-H's), 2.63 (t, 2 H, $J = 6.5$, $\text{C}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}_2$), 0.78-2.13 (several overlapping m, 18 H, other saturated C-H's); mass spectrum (70 eV) m/e (relative intensity) 181.1 (M + 1, 1.3), 180.1 (M, 9.2).

3. Discussion

The procedure that is described above provides an approach to trisubstituted alkenes, compounds that are very common among natural products and which serve as key intermediates in the synthesis of other types of compounds.⁵ The methods that have been developed for the preparation of trisubstituted alkenes are far too numerous to discuss to any significant extent here, but they have been the subject of previous review articles.⁶ Very briefly, however, a large portion of the available methods may be divided among the following categories:⁷ (1) elimination or cleavage reactions of organic halides and other compounds bearing leaving groups; (2) carbonyl condensation reactions of phosphonium ylides and other carbanionic or at least nucleophilic organic intermediates; (3) cleavage or rearrangements of other systems; (4) substitution reactions of alkenyl halides and related compounds;



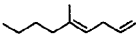
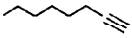

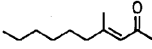

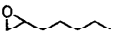
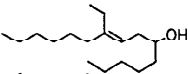
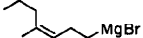

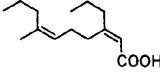



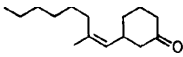
(5) reactions of various allylmetal and other allylic systems; (6) reactions of various alkenylmetal species; and (7) addition reactions to acetylenes, 1,3-dienes, and allenes.

The reaction of organocopper reagents with simple, unactivated acetylenes, an example of the last class of methods in the preceding list, serves as the basis of the procedure described here. This addition reaction was first reported by Normant in 1971⁸ and has been investigated extensively since that time by not only Normant,⁹ but also by Vermeer,¹⁰ Helquist,⁷ Levy,¹¹ and others.^{3b,12} An important modification⁷ of the reaction which has been incorporated in the present preparation is the use of dimethyl sulfide as a ligand and co-solvent which permits much higher yields and a broader range of applicability than the originally reported procedure.⁸

The specific example reported here is one of several preparations that have been developed using the same general reaction sequence. A brief summary of other representative cases is given in Table I.^{7,13} Notice that the alkenylcopper intermediates react with a variety of electrophilic reagents in addition to alkyl halides. It is especially noteworthy that the overall sequences leading to trisubstituted alkenes have been shown to proceed with greater than 99.9% stereoselectivity.⁷ This unusually high degree of control of alkene configuration is of great value in natural products synthesis. The overall stereochemistry is indicative of *syn* addition of the alkylcopper complexes to acetylenes, a result which is observed for several types of carbometallation (or insertion) reactions.⁹

In summary, the procedure described in this chapter is representative of a very general, highly stereoselective approach to trisubstituted alkenes. The usefulness of this methodology has already been demonstrated in total synthesis.^{7,12e,f,h,k,13}

TABLE I
TRISUBSTITUTED ALKENES FROM ADDITION OF GRIGNARD-DERIVED
ALKYL COPPER COMPLEXES TO ACETYLENES,
FOLLOWED BY REACTION WITH ELECTROPHILIC REAGENTS

Grignard Reagent	Acetylene	Electrophile	Product	Overall Yield (%) ^{a, b}
MeMgBr				84
MeMgBr				65
EtMgBr				94
 MgBr		CO ₂		50
 MgBr				73

^aSince yields are sensitive to traces of oxygen during the reactions, the use of an argon atmosphere is strongly recommended.

^bSee refs. 7, 13.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

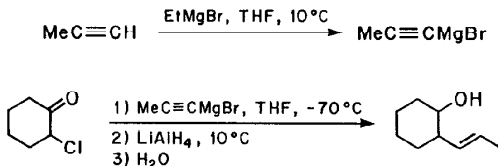
1-Octyne (8,9); (629-05-0)

Dimethyl sulfide: Methyl sulfide (8); Methane, thiobis- (9); (75-18-3)

Hexamethylphosphoric triamide: Phosphoric triamide, hexamethyl- (8,9); (680-31-9)

Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

(Cyclohexanol, 2-(1-propenyl)-, (E)-)

Submitted by P. A. Wender, D. A. Holt, and S. McN. Sieburth.¹

Checked by Peggy A. Radel and Clayton H. Heathcock.

1. Procedure

A dry, 5-L, four-necked, round-bottomed flask is equipped with an air-driven stirrer (Note 1), 250-mL pressure-equalizing dropping funnel, thermometer, rubber septum, and a nitrogen inlet tube which, by means of a T-tube, is also connected to a gas bubbler. After being charged with 1200 mL of anhydrous tetrahydrofuran (Note 2), the flask is swept with dry nitrogen and maintained under an atmosphere of nitrogen throughout the remainder of the reaction. A solution of ethylmagnesium bromide in diethyl ether (1.1 mol, 380 mL, 2.9 M) is transferred to the flask and the flask is then cooled to below 10°C by means of an ice-water bath (Note 3). Propyne is bubbled through the cooled, stirred solution (Note 4) at such a rate that a small amount escapes through the nitrogen inlet/gas bubbler. Propyne addition is continued for 2.5 hr at which time approximately 100 g (2.5 mol) of propyne has been used (Note 5) and the internal temperature has risen $5\text{--}10^\circ\text{C}$. The ice-water bath is then

replaced with a dry ice-acetone bath and the mixture is cooled to ca. -70°C . A solution of 2-chlorocyclohexanone (1 mol, 132.6 g) (Note 6) in 50 mL of tetrahydrofuran is added dropwise from the addition funnel over 1.5 hr so as to maintain the temperature below -65°C (Note 7). After stirring for an additional 1.5 hr at -70°C (Note 8), the dry ice-acetone bath is replaced with an ambient-temperature water bath and the reaction mixture is allowed to warm slowly. When the temperature reaches 10°C , a solution of lithium aluminum hydride in tetrahydrofuran (1 mol, 1000 mL, 1 M) is added by cannula (Note 9). After addition of the lithium aluminum hydride, the mixture is stirred at ambient temperature for 3-5 hr, at which time the solids have dissolved and reaction is complete (Notes 10, 11). The solution is then cooled to 5°C by means of an ice-water bath. The reaction is quenched by careful, dropwise addition of 38 mL of water over 2 hr so that the temperature remains below 20°C . The solution becomes somewhat cloudy at this point and 2000 mL of hexanes is added. The addition of 38 mL of aqueous 15% sodium hydroxide solution over 15 min is followed by the addition of 100 mL of water over 5 min. Some frothing occurs during the last addition of water and a large amount of white aluminum salts precipitates. After 5 min of stirring, 100 g of anhydrous sodium sulfate is added and stirring is continued for another 5 min. The thick mixture is then filtered by suction through Celite using a 200-mm diameter Büchner funnel. The solids are removed from the funnel, thoroughly washed with 1500 mL of hot tetrahydrofuran (Note 12), and re-filtered. This wash is repeated twice and the combined organic solutions are concentrated with a rotary evaporator (15 mm). The residual yellow liquid is distilled under reduced pressure to yield 118.8 g (85%) of 2-E-propenylcyclohexanol as a clear colorless liquid, bp $49-54^{\circ}\text{C}$ (1 mm) (Note 13).

2. Notes

1. The use of a magnetic stirrer is more convenient than a mechanical stirrer for reactions conducted on small scale (<0.2 mol) or at low concentrations (<0.5 M). However, because of the difficulty encountered in stirring the sometimes thick suspensions associated with concentrated (e.g. 1 M) reaction mixtures, and because of the potentially disastrous results if a stir bar should fracture the flask wall during a large scale preparation, the submitters strongly recommend the use of an air-driven overhead mechanical stirrer for such large scale reactions. At a later stage in the reaction, when the propynylmagnesium bromide is cooled to -70°C , the THF solution becomes viscous and rather difficult to stir. The checkers recommend the use of a heavy-duty, air-driven stirrer such as the Fisher Scientific model 14-508-5. An electrically driven overhead stirrer should not be used, as the hydrogen released during the quench represents a considerable explosion hazard.

2. The submitters used 'Baker Analyzed' tetrahydrofuran (0.005% H_2O) without further purification or drying.

3. The submitters used ethylmagnesium bromide solution purchased from Aldrich Chemical Company, Inc., and found it most convenient to measure the required amount by transferring the solution by cannula to a nitrogen-flushed graduated cylinder fitted with a rubber septum. This measured amount of solution is then transferred to the flask by cannula. See reference 2 for general techniques for handling air-sensitive reagents in this manner. Some of the Grignard reagent precipitates at this temperature and concentration. There is a tendency for the ethylmagnesium bromide to clog the cannula. The checkers found it convenient to use a cannula made from 2-mm stainless steel tubing.

4. Propyne of 99.96% purity, purchased from Liquid Carbonic Company in a lecture bottle, was used without purification and was introduced to the flask by means of a Tygon tube which was attached to a 9-inch, 18-gauge hypodermic needle.

5. The amount of propyne used is conveniently determined by weighing the lecture bottle before and after addition. In this case the submitters used an excess of alkyne to insure complete consumption of the Grignard reagent. In cases where non-gaseous, non-volatile alkynes are to be used, stoichiometric amounts suffice.

6. The submitters used 2-chlorocyclohexanone purchased from Aldrich Chemical Company, Inc., without further purification. Alternatively, this compound can be easily prepared by chlorination of cyclohexanone.³

7. A flask should be used that is constructed in such a manner that the chloro ketone solution drips directly from the addition funnel into the reaction mixture. Any portion that flows along the sides of the flask will freeze.

8. Chloro alkoxide formation is essentially complete at this time and can be conveniently monitored by quenching a small aliquot and subjecting it to GLC analysis. Using a 50 m x 0.2 mm OV-1 capillary column at 110°C and a flow rate of 0.87 mL/min (H_2 carrier) the submitters found retention times of 3.2 min for 2-chlorocyclohexanone and 6.7 min and 7.2 min for trans- and cis-1-propynyl-2-chlorocyclohexanols, respectively.

9. Lithium aluminum hydride in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc., and was handled in the fashion described above for the Grignard solution (see Note 3). While solid lithium aluminum hydride can be used (with appropriate changes in the amount of solvent initially used), the hazards of handling this flammable and even explosive reagent (see references 4 and 5) can be reduced by using the pre-prepared solution.

An excess of hydride reagent is necessary to facilitate complete reaction in a reasonable time. When only the stoichiometric amounts of hydride reagent are used, the reaction is not complete even after several days at room temperature.

10. In reactions run at high concentration the reaction has a tendency to become slightly exothermic at some point, with the temperature increasing as much as 30°C. Although the reaction is usually complete in less time, and with no reduction in yield of product, this exothermic reaction can be prevented by keeping the flask in a large ambient-temperature water bath, thus buffering temperature changes that apparently initiate the exothermic reaction. The progress of the reaction can be conveniently monitored by TLC or GLC analysis of a quenched aliquot. Using the same GLC conditions as described in Note 8, the retention times for cis- and trans-2-E-propenylcyclohexanols are 4.1 min and 3.9 min, respectively.

11. The checkers noted that a homogeneous solution occurs after about 2 hr. However, TLC and GLC analysis showed that reaction was not complete until 3.5 to 5 hr.

12. The tetrahydrofuran used for washing the filter cake should be tested for peroxides before use, since the final distillation is carried out almost to dryness.

13. GLC analysis indicated a purity greater than 98% and a cis to trans ratio of 1:2. These isomers can be separated by column chromatography and give the following ^1H NMR spectra: (CDCl_3) δ : cis: 1.1-2.0 (m, 12 H, CH_2 , CH_3 , OH), 2.2 (m, 1 H, allylic CH), 3.75 (m, 1 H, carbinol CH), 5.4-5.6 (m, 2 H, $\text{CH}=\text{CH}$); trans: 1.0-2.2 (m, 10 H, CH_2 , OH, allylic CH), 1.70 (d, 3 H, $\text{J} = 4.9$, CH_3), 3.1 (m, 1 H, carbinol CH), 5.0-5.8 (m, 2 H, $\text{CH}=\text{CH}$).

3. Discussion

A variety of approaches have been employed to effect the preparation of α -alkenyl ketones and carbinols, including reactions of metallo alkenes with epoxides,⁶ α -halo ketones,⁷ or enolonium ion equivalents⁸ and the reactions of ketone enolates with vinyl cation equivalents.⁹ The procedure described here offers several advantages over existing methodology. Starting materials and reagents are all commercially available at low cost. Manipulations are simple and the procedure can be carried out in a single operation, in a single flask, on a small or large (1 mol) scale and in high yield. In addition, as described in more detail elsewhere,¹⁰ this method permits the use of cyclic as well as acyclic halo ketones, bromo ketones instead of chloro ketones, a variety of alkynes including acetylene, conjugated alkynes, and 3-silyloxy functionalized alkynes, and other aluminum hydride reagents such as diisobutylaluminum hydride and lithium trimethoxyaluminum hydride. Furthermore, the method provides for complete control over alkene geometry and easy access to trisubstituted alkenes of defined stereochemistry.

Mechanistically, the reaction proceeds through an alkynyl chloro alkoxide which, when treated with the reducing agent, is hydroaluminated to yield the vinyl alenate, which subsequently undergoes a facile pinacol-like 1,2-rearrangement. Excess hydride reagent reduces the intermediate alkenyl ketone and the resulting 2-alkenyl carbinol is isolated upon aqueous workup (Scheme). Table I contains representative examples.

1. Department of Chemistry, Harvard University, Cambridge, MA 02138 and Department of Chemistry, Stanford University, Stanford, CA 94305.

2. Aldrich Chemical Company, Inc., Bulletin No. A74. "Handling Air-Sensitive Solutions."
3. Newman, M. S.; Farbman, M. D.; Hipsher, H. *Org. Synth., Collect. Vol. III* 1955, 188.
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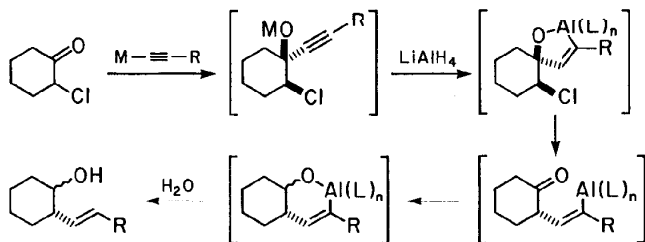


TABLE I
PREPARATION OF ALKENYL CARBINOLS

Carbonyl	Alkynylide	Alkenyl Carbinol	Yield (%)
	$-C\equiv C-MgBr$		85
	$CH_2=CH-C\equiv C-Li$		71
	$(CH_3)_2CH-C\equiv C-Li$		76
	$CH_2=CH-C\equiv C-Li$		91
	$(CH_3)_2CH-C\equiv C-Li$		46

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2-E-Propenylcyclohexanol: Cyclohexanol, 2-(1-propenyl)-, [1 α ,2 α (E)]- (11); (76123-38-1); [1 α ,2 β (E)]- (1); (76156-39-3)

Ethylmagnesium bromide: Magnesium, bromoethyl- (9); (925-90-6)

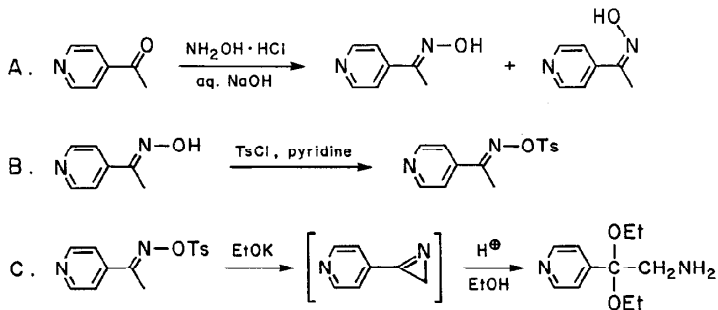
Propyne (8); 1-Propyne (9); (74-99-7)

2-Chlorocyclohexanone: Cyclohexanone, 2-chloro- (8,9); (822-87-7)

Lithium aluminum hydride: Aluminate (1-), tetrahydro-, lithium (8); Aluminate (1-), tetrahydro-, lithium, (1-4)- (9); (16853-85-3)

α -AMINO ACETALS: 2,2-DIETHOXY-2-(4-PYRIDYL)ETHYLAMINE

(4-Pyridineethanamine, β,β -diethoxy)



Submitted by John L. LaMattina and R. T. Sulesko.¹

Checked by Paul Hebeisen and Andrew S. Kende.

1. Procedure

A. *4-Acetylpyridine oxime.* Hydroxylamine hydrochloride (25.0 g, 0.36 mol) (Note 1) is dissolved in 50 mL of water, and the solution is added to 70 mL of 20% aqueous sodium hydroxide in a 500-mL Erlenmeyer flask. To this magnetically stirred solution is added at one time 4-acetylpyridine (36.3 g, 0.30 mol) (Note 2); a precipitate forms rapidly. The reaction mixture is stirred at 0-5°C for 2 hr; then the precipitate is collected by suction filtration and washed with 500 mL of cold water.

The product (mp 122-146°C, 33-36 g, 81-88%) can be shown from its ^1H NMR spectrum (Note 3) to be a 5:1 mixture of the E- and Z-isomer of 4-acetylpyridine oxime. To obtain pure E-isomer (Note 4), the product is recrystallized twice as follows. The crude product is dissolved in 600 mL of hot water in a 2-L Erlenmeyer flask, the hot solution decanted from any undissolved residue, and the supernatant liquid is allowed to cool slowly to 30°C during 2-3 hr by placing the flask on a cork ring. The precipitate is collected at this temperature by suction filtration. A second crystallization by the same procedure yields pure E-oxime, which is dried under reduced pressure over Drierite to constant weight. The yield of E-4-acetylpyridine oxime, mp 154-157°C, (Note 5) is 27.1-28.3 g (66-69%).

B. 4-Acetylpyridine oxime tosylate. Pure E-oxime (27.1 g, 0.20 mol) and p-toluenesulfonyl chloride (47.9 g, 0.22 mol) (Note 6) are added to 100 mL of anhydrous pyridine (Note 7) in a 1-L, round-bottomed flask fitted with a drying tube and a large magnetic stirring bar. The reaction mixture is stirred at 25°C for 24 hr; a precipitate of pyridine hydrochloride forms. A 500-mL portion of ice water is added with continued stirring. The initial precipitate dissolves and a voluminous white precipitate soon forms. This is collected by suction filtration, washed with three 150-mL portions of cold water and dried under reduced pressure and over Drierite to constant weight. The yield of pure tosylate, mp 79-81°C (Note 8), is 55.1 g (95%).

C. 2,2-Diethoxy-2-(4-pyridyl)ethylamine. To a 2-L, round-bottomed flask containing 80 mL of absolute ethanol (Note 9) and fitted with a magnetic stirrer and a reflux condenser with a drying tube is slowly added potassium metal (7.60 g, 0.19 mol) (Note 10). When the metal has dissolved, the solution is cooled to 0-5°C and E-4-acetylpyridine tosylate (55.1 g, 0.19 mol)

dissolved (with gentle warming) in 320 mL of absolute ethanol is added over 15 min through a dropping funnel to the stirred solution at 0-5°C. During this period a precipitate of potassium p-toluenesulfonate forms. The temperature of the stirred mixture is allowed to rise to room temperature for 1 hr. The mixture is diluted with 1 L of anhydrous ether and filtered by suction. The precipitate is quickly washed with 150 mL of anhydrous ether. The ether filtrates are combined, and hydrogen chloride gas is bubbled through the ether solution for 15 min. A precipitate forms immediately. The precipitate is collected by suction filtration, washed with three 170-mL portions of anhydrous ether and dried briefly under reduced pressure. The dihydrochloride thus obtained is dissolved in 200 mL of water, and powdered sodium carbonate is added until the mixture reaches a pH of >10. The mixture is extracted four times with 125-mL portions of chloroform. The combined chloroform extracts are dried over anhydrous magnesium sulfate and concentrated at reduced pressure to an oil. This orange-red oil is distilled at 0.2 mm to yield 29.7 g (74.5%) of the amine as a colorless oil, bp 93-95°C (Note 11).

2. Notes

1. Hydroxylamine hydrochloride 97% (mp 155-157°C), available from Aldrich Chemical Company, Inc. or Fisher Scientific Company, is suitable for use without further purification.

2. 4-Acetylpyridine (98%) from Aldrich Chemical Company, Inc. was distilled under reduced pressure (bp 103-104°C/14-16 mm) prior to use.

3. In dimethyl sulfoxide- d_6 , the E- and Z-isomers show 1H proton resonances at δ 11.65 and 10.97, respectively.

4. Use of the isomer mixture prevents isolation of oxime tosylate in crystalline form at the next step and leads to reduced overall yield of pure amine.

5. The lit² mp for the oxime is 158°C.

6. p-Toluenesulfonyl chloride was purified prior to use by the procedure of L. Fieser and M. Fieser in "Reagents for Organic Syntheses."³

7. Pyridine AR (Mallinckrodt, Inc.) was used directly.

8. The lit² mp for this compound is 80°C.

9. Ethanol was dried by reflux over magnesium ribbon.

10. For the safe handling and disposal of potassium metal, see *Org. Synth., Collect. Vol. IV 1963*, 134.

11. This compound has the following 90 MHz ¹H NMR spectrum (CDCl₃) δ: 8.58 (d of d, 2 H, J = 2, 4.5, pyridine H₂ and H₆), 7.37 (d of d, 2 H, J = 2, 4.5, pyridine H₃ and H₅), 3.41 [m, 4 H, (OCH₂CH₃)₂], 2.97 (s, 2 H, CH₂NH₂), 1.20 [t, 6 H, J = 7, (CH₃CH₂O)₂], 0.75 (br s, 2 H, NH₂). Anal. Calcd for C₁₁H₁₈N₂O₂: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.63; H, 8.52; N, 13.20.

3. Discussion

α-Amino ketones are useful intermediates for the preparation of a variety of heterocycles including imidazoles,⁴ oxazoles,⁵ and pyrazines.⁶ Unfortunately, pyrazine formation can be a complicating side reaction because of the tendency of α-amino ketones to dimerize. One way to avoid this problem is to generate these intermediates in a protected form, specifically, as α-amino acetals.⁷ Such derivatives allow one to manipulate the amino moiety as desired. The acetal can then be hydrolyzed at the appropriate interval to complete the synthesis.

α -Amino acetals have previously been prepared via catalytic hydrogenation of α,α -dialkoynitriles,⁸ a method which is limited by the availability of the appropriate starting material. The procedure here offers a more simple approach which involves the Neber rearrangement. Although this reaction is generally used to prepare α -amino ketones, use of an anhydrous ethanol medium readily results in acetal formation. A summary of other α -amino acetals prepared using this procedure appears in the Table.

This reaction, like all Neber rearrangements, is limited by availability of the appropriate oxime tosylate.⁹ Substrates in which the aryl group contain an electron-donating function are unstable, since they have a propensity to undergo Beckmann rearrangement. However, this difficulty can be resolved by subsequent conversion of the α -amino acetals. For example, catalytic hydrogenation of 2,2-diethoxy-2-(p-bromophenyl)ethylamine yields the known parent compound, 2,2-diethoxy-2-phenylethylamine. These two α -amino acetals readily undergo hydrolysis and should be protected from moisture.

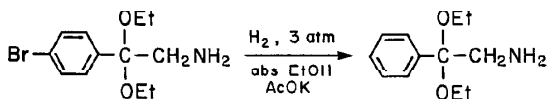
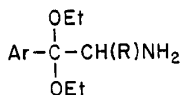


TABLE I
PREPARATION OF α -AMINO ACETALS



Ar	R	Yield (%)	bp °C/mm	mp °C, HCl salt
2-pyridyl	H	58	82/0.2	150 (dec) ^a
3-pyridyl	H	53	84/0.2	187-188 ^a
4-pyridyl	CH ₃ ^b	40	98/0.2	129-130 ^a
4 O ₂ N-C ₆ H ₄	H	78	c	116 (dec)
4-Br-C ₆ H ₄	H	92	d	

a. Dihydrochloride salt.

b. For the preparation of this material in Step C, gaseous HCl is bubbled into the ethereal filtrate for 3 hr. Presumably the longer reaction time is necessary for steric reasons.

c. This material decomposes on distillation, and is purified by column chromatography (silica gel/chloroform).

d. This material decomposes on distillation and hydrolyzes when chromatographed on silica gel. However, ¹H-NMR analysis indicates that it is >95% pure.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2,2-Diethoxy-2-(4-pyridyl)ethylamine: 4-Pyridineethanamine,

β,β -diethyl (10); (74209-44-2)

4-Acetylpyridine: Ketone, methyl 4-pyridyl (8); Ethanone, 1-(4-pyridinyl)- (9); (1122-64-9)

Hydroxylamine hydrochloride (8); Hydroxylamine, hydrochloride (9); (5470-11-1)

4-Acetylpyridine oxime: Ketone, methyl 4-pyridyl oxime (8); Ethanone, 1-(4-pyridinyl)- oxime (9); (1194-99-6)

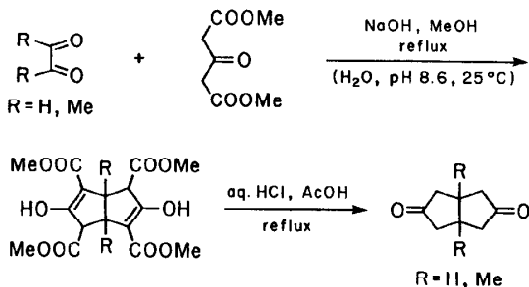
p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

4-Acetylpyridine oxime tosylate: Ethanone, 1-(4-pyridinyl)-O-[(4-methylphenyl)sulfonyl]oxime (10); (74209-52-2)

CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH 1,2-DICARBONYL

COMPOUNDS: *cis*-BICYCLO[3.3.0]OCTANE-3,7-DIONES

(2,5(1H,3H)-Pentalenedione, tetrahydro-, *cis*- and 2,5(1H,3H)-pentalenedione, tetrahydro-, 3a,6a-dimethyl-, *cis*)



Submitted by Steven H. Bertz,¹ James M. Cook,² Ali Gawish,² and Ulrich Weiss.³

Checked by Todd K. Jones, Scott E. Denmark, S. V. Govindan, and Robert M. Coates.

1. Procedure

I. Specific procedure for glyoxal:

A. *Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate*. A 3-L, three-necked, round-bottomed flask is equipped with a thermometer, mechanical stirrer, pressure-equalizing dropping funnel, reflux condenser, and a heating mantle (Note 1). A solution of 64 g (1.60 mol) of

sodium hydroxide (Note 2) in 1.15 L of methanol is prepared in the flask, cooled in an ice bath, and stirred as 273 g (1.57 mol) of dimethyl 1,3-acetonedicarboxylate (Note 3) is added dropwise. The resulting slurry is stirred and heated to reflux at which point the white salt dissolves. The heating mantle is removed, and the solution is stirred rapidly while 128.5 g of aqueous 40% glyoxal (51.4 g, 0.886 mol) (Notes 3 and 4) is added at a rate sufficient to maintain the internal temperature at 65°C (Note 5). After the addition is completed (40-60 min, Note 6), the mixture is allowed to cool to room temperature and stirred overnight (Note 7). The precipitate is collected by suction filtration, washed with 500 mL of methanol (Note 8), and dried under reduced pressure. The yield of the white to light yellow disodium salt is 197-215 g (58-63%) (Note 9).

A 6-L Erlenmeyer flask equipped with a large magnetic stirring bar (Note 10) is charged with 1 L of chloroform and a solution of the disodium salt (0.46-0.50 mol) in 800 mL of water. The two phase mixture is stirred rapidly as 2.00 equiv (920-1000 mL, 0.92-1.00 mol) of cold 1 M hydrochloric acid is added. The layers are separated and the aqueous phase is extracted with three 500-mL portions of chloroform. The combined organic layers are washed once with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure by rotary evaporation keeping the water bath temperature at or below 40°C. Crystallization of the remaining waxy solid from 2:1 hexane-ethyl acetate affords 158-171 g (54-59% based on dimethyl 1,3-acetonedicarboxylate) of the tetraester, mp 97-100°C (Note 11).

B. *cis-Bicyclo[3.3.0]octane-3,7-dione*. A 3-L, three-necked, round-bottomed flask equipped with a heating mantle, two reflux condensers, and a magnetic stirrer (Note 12) is charged with 135 g (0.364 mol) of the tetraester, 66 mL of glacial acetic acid, and 600 mL of 1 M hydrochloric acid

(Note 13). The mixture is stirred vigorously and heated at reflux for 2.5 hr (Note 14). The solution is cooled in an ice bath and the product is extracted with five 250-mL portions of chloroform. The chloroform extracts are combined, and the solution is concentrated by rotary evaporation (bath temperature at or below 40°C) until most of the acetic acid is removed. The residue is dissolved in 300 mL of fresh chloroform. The solution is washed with 60-mL portions of saturated sodium bicarbonate until the aqueous layer remains basic to litmus paper, dried with anhydrous sodium sulfate, and evaporated cautiously under reduced pressure. The yield of 44-45.5 g (88-90%) of white to light yellow solid, mp 84-85°C (Note 15). The product is sufficiently pure for most purposes; it may be purified by recrystallization from methanol or ethanol and/or by sublimation at 70°C (0.1 mm).

II. General procedure using aqueous buffer:

A. *Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo[3.3.0]octa-8,9-diene-2,4,6,8-tetracarboxylate*. A freshly prepared solution (pH 8.3) of 5.6 g of sodium bicarbonate in 400 mL of water, 70 g (0.40 mol) of dimethyl 1,3-acetonedicarboxylate, and a magnetic stirring bar are placed in a 1-L Erlenmeyer flask. The resulting solution is stirred rapidly as 17.2 g (0.20 mol) of biacetyl (Note 3) is added in one portion. Stirring is continued for 24 hr during which time white crystals separate. The solid is collected by suction filtration and dried under reduced pressure to afford 60-62 g, mp 155-158°C. The filtrate is cooled in an ice bath, acidified to pH 5 (pHydron paper) with dilute hydrochloric acid, and extracted with three 100-mL portions of chloroform. The chloroform extracts are combined, washed with saturated sodium chloride, and dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gives another 2-4 g of crude product (Note 16). Recrystallization from hot methanol gives 58-60 g (73-75%) of the tetraester, mp 155-157°C, in two crops (Note 17).

B. *cis*-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione. A 1-L, one-necked, round-bottomed flask is equipped with a heating mantle, reflux condenser, and a magnetic stirring bar. The flask is charged with 200 mL of 1 M hydrochloric acid, 40 mL of glacial acetic acid, and 24 g (0.060 mol) of the tetraester from Part IIA. The mixture is stirred vigorously and heated at reflux for 3-6 hr (Note 18). The solution is cooled in an ice bath and the product is isolated as described in Part IB above. The yield of white to light yellow solid, mp 219-221°C, is 9.5-9.8 g (95-98%). Recrystallization from a minimum amount of hot ethanol affords 7.5-7.7 g (75-77%) of the diketone, mp 222-225°C, in one crop (Note 19).

2. Notes

1. The dropping funnel and the reflux condenser were connected to the same neck using a Claisen adapter.

2. The submitters recommend that a high-purity grade of sodium hydroxide be used. *Otherwise insoluble impurities are formed that must be removed by filtration through a sintered glass Buchner funnel.*

3. Dimethyl 1,3-acetonedicarboxylate, aqueous 40% glyoxal, and biacetyl were purchased from Aldrich Chemical Company, Inc. The submitters advise against using glyoxal solution that contains a significant amount of white solid.

4. The submitters report that the yield is decreased by 5% if exactly 0.5 equiv of glyoxal is used. The yield is improved to 75-76% in runs carried out on smaller scale (ca. 0.1 mol of glyoxal).

5. Heating should be resumed if necessary to maintain a temperature of 65°C. The submitters report that lower yields are obtained at lower temperatures (e.g., 37% at 25°C).

6. The submitters caution that the addition time is critical. In one run by the checkers with a 30-min addition time, the yield of the disodium salt was reduced to 49%.

7. Similar yields were obtained by the submitters when the reaction mixture was allowed to cool at room temperature for 2 hr and in an ice bath for another 2 hr.

8. The solid is washed first by allowing methanol to percolate through the filter cake with gentle suction until the brown color is removed. The product is suspended in methanol, filtered, and washed again by the percolation procedure.

9. The submitters obtained 411-430 g (61-64%) from reactions conducted on twice the scale described using a 2-hr addition time. Elemental analyses by the submitters and checkers indicate a variable degree of hydration ($n = 1-2$) for the product. The yield and molar quantities of the disodium salt are calculated assuming a monohydrate, $C_{16}H_{16}O_{10}Na_2H_2O$. For further characterization of this salt, see ref. 6.

10. The checkers used a mechanical stirrer to achieve more efficient mixing of the layers.

11. The submitters obtained 176-182 g (62-64%) of product, mp 103-105°C, after trituration with a minimum amount of cold methanol. Crystallization was facilitated by scraping the sticky solid with a silver spatula. The reported melting point is 104-107°C.⁴ The crude product obtained initially by the checkers was a low melting solid, mp 70-75°C, that was conveniently transferred and purified by recrystallization from about 1 L of hot 2:1 hexane-ethyl acetate. Elemental analyses of the product by the submitters were within $\pm 0.4\%$ of the theoretical value. The spectral properties of the product are as follows: IR ($CHCl_3$) cm^{-1} : 1740, 1673, 1632, 1450, 1438, 1250,

1200, 1155; ^1H NMR (CDCl_3 , 200 MHz) δ : 3.64 (apparent t, 2 H, $J_{\text{app}} = 2.4$, two CH), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.87 (apparent t, 2 H, $J_{\text{app}} = 2.4$, two CH), 10.35 (broad s, 2 H, two enolic OH).

12. The volume of the flask should be at least three times larger than the volume of the solution to avoid losses from excessive foaming caused by rapid evolution of carbon dioxide. The checkers used a mechanical stirrer to facilitate stirring of the initially heterogeneous mixture.

13. The submitters point out that the disodium salt may be used directly provided that two additional equivalents of 1 M hydrochloric acid are employed. Acetic acid may be omitted to simplify the isolation procedure. In this case the reaction mixture remains heterogeneous throughout.

14. Progress of the reaction can be followed by observing the gas evolved through a bubbler connected to the top of the reflux condenser.

15. The product gave satisfactory elemental analyses: Calcd for $\text{C}_8\text{H}_{10}\text{O}_2$: C, 69.54, H, 7.30. Found: C, 69.42; H, 7.36. The literature melting point is 84–86°C.⁴ The spectral properties of the product are as follows: IR (CHCl_3) cm^{-1} : 1738 (C=O), 1406, 1222, 1208, 1176, 792; ^1H NMR (CDCl_3 , 220 MHz) δ : 2.16 (dd, 4 H, $J = 4.2, 19.3$, H_A of $\text{CH}_\text{A}\text{H}_\text{B}$), 2.59 (dd, 4 H, $J = 8.5, 19.3$, H_B of $\text{CH}_\text{A}\text{H}_\text{B}$), 3.04 (m, 2 H, CH); ^{13}C NMR (CDCl_3) δ : 35.5 (d, CH), 42.63 (t, CH_2), 217.2 (s, C=O); mass spectrum (70 eV) m/e (rel intensity): 138 (M^+ , 41), 69 (36), 68 (58), 41 (100), 39 (53).

16. The checkers obtained ca. 19 g of a viscous red oil which, upon dissolution in ca. 150 mL of methanol, deposited 4 g of crude crystalline product.

17. The product gave a satisfactory elemental analysis: Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_{10}$: C, 54.28; H, 5.53. Found: C, 54.00; H, 5.57. The melting point reported initially (167–169°C after sublimation)⁵ is evidently incorrect. The

spectral properties of the product are as follows: IR (KBr) cm^{-1} : 3539, 1742, 1664, 1425, 1340, 1260, 1235, 1070, 1020; ^1H NMR (CDCl_3) δ : 1.29 (s, 6 H, two CH_3), 3.75 (s, 6 H, two CO_2CH_3), 3.87 (s, 6 H, two CO_2CH_3), 3.94 (s, 2 H, two CHCO_2CH_3), 10.62 (br s, 2 H, two OH).

18. The checkers recovered a 1:1 mixture of tetraester and diketone from two runs conducted for 2.5 hr. When the reflux time was extended to 6 hr, complete conversion to product was attained. The reaction progress was monitored by gas evolution (Note 14). Some variability of reaction times is probably attributable to differences in stirring efficiency, temperature gradients, and/or particle size of the crystalline starting material.

19. The recrystallized product was analyzed by the checkers. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.54. The spectral properties of the product are as follows: IR (KBr) cm^{-1} : 1736, 1390, 1245, 1210, 1180, 1145, 1070; ^1H NMR (CDCl_3 , 360 MHz) δ : 1.22 (s, 6 H, two CH_3), 2.36 and 2.39 (AB q, 8 H, $J = 18.5$, four CH_2).

3. Discussion

Bicyclo[3.3.0]octane-3,7-dione has been prepared in five steps from dimethyl malonate and chloral in about 20% overall yield.⁴ The direct formation of bicyclo[3.3.0]octane-3,7-diones by the 2:1 condensation of acetone-1,3-dicarboxylate and 1,2-dicarbonyl compound was discovered by Weiss and Edwards.⁵ The variation described in Part I has been optimized for large-scale preparation of the parent diketone.⁶ It is a good example of what Turner⁷ has called a "point reaction," as it is very sensitive to experimental details such as temperature and stirring rate. The aqueous buffer procedure given in Part II is a "plateau reaction,"⁷ and affords a general method for

preparing a variety of angularly-substituted bicyclo[3.3.0]octane-3,7-diones (Table I).⁸⁻¹⁵ The parent dikeone can also be prepared by the aqueous buffer procedure (Part II), but chromatography is required to purify the product.¹³ The mechanism of this novel annulation reaction involves a complex sequence of aldol condensations, dehydrations, and Michael additions,^{9,16,17} the order of which may be pH dependent.¹⁷ The isolation of γ -hydroxycyclopentenones in certain cases^{9,16} implicates these reactive Michael acceptors as intermediates. A number of other interesting products have been isolated from reaction of glyoxal with acetonedicarboxylate.^{17,18} The various bicyclic diketones prepared by this method have served as starting materials for syntheses of polycyclic compounds¹⁹ and natural products.²⁰

TABLE I
2:1 CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE
WITH VARIOUS 1,2-DICARBONYL COMPOUNDS

$\begin{array}{c} \text{R} \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{R}' \end{array}$		Yield (%)	Ref.
Glyoxal	$\text{R} - \text{R}' = \text{H}$	70	6,13
Pyruvaldehyde	$\text{R} = \text{H}, \text{R}' = \text{CH}_3$	52	5
Phenylglyoxal	$\text{R} = \text{H}, \text{R}' = \text{Ph}$	66	9
3-Cyclopentenylglyoxal	$\text{R} = \text{C}_5\text{H}_7, \text{R}' = \text{H}$	90	15
4-Cycloheptenylglyoxal	$\text{R} = \text{C}_7\text{H}_{11}, \text{R}' = \text{H}$	70	15
1-Phenyl-1,2-propanedione	$\text{R} = \text{CH}_3, \text{R}' = \text{Ph}$	68	15
4,5-Dioxopentanoic Acid	$\text{R} = \text{H}, \text{R}' = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	80	8
Biacetyl	$\text{R} = \text{R}' = \text{CH}_3$	84	5
2,3-Pentanedione	$\text{R} = \text{CH}_3, \text{R}' = \text{CH}_2\text{CH}_3$	70	15
2,3-Hexanedione	$\text{R} = \text{CH}_3, \text{R}' = \text{CH}_2\text{CH}_2\text{CH}_3$	64	15
Cyclopentane-1,2-dione	$\text{R}-\text{R}' = (\text{CH}_2)_3$	45	5,14
Cyclohexane-1,2-dione	$\text{R}-\text{R}' = (\text{CH}_2)_4$	81	10
Cyclooctane-1,2-dione	$\text{R}-\text{R}' = (\text{CH}_2)_6$	80	11
Cyclooct-5-ene-1,2-dione	$\text{R}-\text{R}' = (\text{CH}_2)_2\text{CHCH}(\text{CH}_2)_2$	87	12
Cyclododecane-1,2-dione	$\text{R}-\text{R}' = (\text{CH}_2)_{10}$	94	11
Ninhydrin	$\text{R}-\text{R}' = \text{C}_7\text{H}_4\text{O}$	60	9

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Dimethyl 1,3-acetonedicarboxylate: Glutaric acid, 3-oxo-, dimethyl ester (8);
Pentanedioic acid, 3-oxo-, dimethyl ester (9); (1830-54-2)
Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-
tetracarboxylate: 1,3,4,6-Pentalenetetracarboxylic acid, 1,3a,4,6a-
tetrahydro-2,5-dihydroxy-, tetramethyl ester, (1 α ,3 α ,4 α ,6 α)-
(11); (82416-04-4)
Glyoxal (8); Ethanedial (9); (107-22-2)

cis-Bicyclo[3.3.0]octane-3,7-dione: 2,5(1H,3H)-Pentalenedione, tetrahydro-, cis- (9); (51716-63-3)

Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo-[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate: 1,3,4,6-Pentalenetetracarboxylic acid, 1,3a,4,6a-tetrahydro-2,5-dihydroxy-3a,6a-dimethyl-, tetramethyl ester (11); (79150-94-0)

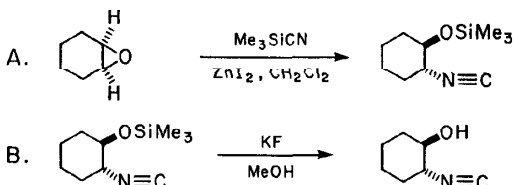
Biacetyl: 2,3-Butanedione (8,9); (431-03-8)

cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione: 2,5(1H,3H)-Pentalenedione, tetrahydro-3a,6a-dimethyl-, cis- (9); (21170-10-5)

CONVERSION OF EPOXIDES TO β -HYDROXY ISOCYANIDES.

TRANS-2-ISOCYANOCYCLOHEXANOL

(Cyclohexanol, 2-isocyanato-, trans-)



Submitted by Paul G. Gassman and Thomas L. Guggenheim.¹

Checked by Curtis E. Adams and K. Barry Sharpless.

1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. [(trans-2-Isocyanocyclohexyl)oxy]trimethylsilane. A 100-mL, three-necked flask equipped with a reflux condenser, constant pressure dropping funnel, magnetic stirring bar, and drying tube is charged with 20.2 g (204 mmol) of trimethylsilyl cyanide (Note 1), 60 mg (0.19 mmol) of anhydrous zinc iodide (Note 2) and 5 mL of dry methylene chloride (Note 3). The constant pressure dropping funnel is charged with 10.0 g (102 mmol) of cyclohexene oxide (Note 4) and 5 mL of dry methylene chloride. The reaction mixture is heated to reflux and the cyclohexene oxide - methylene chloride solution is added dropwise to the refluxing reaction mixture over a 30-min period. After the addition is complete, the reaction mixture is refluxed for 4 hr and then

allowed to cool to room temperature. The reaction mixture is transferred to a one-necked flask and the solvent and excess trimethylsilyl cyanide are removed under reduced pressure on a rotary evaporator (Note 5). The residue is vacuum distilled through a 3-inch Vigreux distillation column to yield 15.74 g (78%) of [(trans-2-isocyanocyclohexyl)oxy]trimethylsilane, bp 69-70°C (1.5 mm) (Note 6).

B. *trans*-2-Isocyanocyclohexanol. A 250-mL, one-necked, round-bottomed flask is charged with 13.72 g (70 mmol) of [(trans-2-isocyanocyclohexyl)oxy]-trimethylsilane, 12.12 g (210 mmol) of potassium fluoride (Note 7), and 100 mL of methanol. The reaction mixture is stirred magnetically for 5 hr at room temperature (23°C). The methanol is removed under reduced pressure on a rotary evaporator to yield a white slurry. This slurry is added to the top of a 250-g, 60-200 mesh silica gel chromatography column and the column is eluted with 20% ethyl acetate - 80% hexane solvent mixture (Note 8). The solvent is removed from those fractions containing the product under reduced pressure on a rotary evaporator to afford an oil which is redissolved in methylene chloride and the solution is filtered. The methylene chloride is removed from the filtrate under reduced pressure on a rotary evaporator to yield 8.46 g (68 mmol, 97%) of white, crystalline *trans*-2-isocyanocyclohexanol, mp 57.0-59.5°C (Note 9).

2. Notes

1. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth.* 1980, 60, 126-132. The checkers used trimethylsilyl cyanide as supplied from Aldrich Chemical Company, Inc.

2. Anhydrous zinc iodide was purchased from Alfa Products, Morton/Thiokol, Inc., and used without further purification. In one run the checkers used 0.25 mmol of ZnI_2 and obtained a better yield than when they used 0.19 mmol of ZnI_2 (84% yield instead of 73%).

3. Commercial methylene chloride is dried by distillation from calcium hydride prior to use.

4. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc., and was used without purification.

5. The checkers also carried out this process in a fume hood. All glassware was rinsed afterwards with 10% KOH solution or rinsed with acetone and the rinses mixed with 10% KOH. The resulting KOH solutions were treated with Chlorox overnight before being discarded.

6. This pure, colorless liquid showed The following physical properties: IR (neat) cm^{-1} : 2950, 2870, 2145, 1454, 1267, 1255, 1144, 1114, 1065, 1028, 931, 894, 884, 844 and 758; ^1H NMR (60 MHz, CDCl_3/TMS) δ : 3.73-3.00 (br m, 2 H), 2.30-0.95 (br m, 8 H), 0.17 (s, 9 H); ^1H NMR (250 MHz, $\text{CDCl}_3/\text{CHCl}_3$ @ 7.24) δ : 3.56 (m, 1 H), 3.28 (m, 1 H), 2.13 (m, 1 H), 1.86 (m, 1 H), 1.67 (m, 2 H), 1.56 (m, 1 H), 1.25 (m, 3 H), 0.15 (s, 9 H); density 0.882 g/mL.

7. Potassium fluoride was purchased from the Fisher Scientific Company.

8. Approximately 100-mL fractions are collected. The progress of the chromatography is followed by analysis of the eluting fractions with thin-layer chromatography developed with iodine vapor. The checkers achieved equal success using 120 g of 70-230 mesh silica in a 30 x 250-mm column.

9. The product showed the following physical properties: IR (KBr) cm^{-1} : 3470, 3400, 2965, 2945, 2870, 2175, 1450, 1376, 1328, 1302, 1240, 1123, 1090, 1081, 1007, 919, 856, and 851; ^1H NMR (60 MHz, CDCl_3/TMS) δ : 3.90-3.00

(br m, 2 H), 2.85 (d, 1 H, J = 5), 2.40-0.70 (br m, 8 H); ^1H NMR (250 MHz, $\text{CDCl}_3/\text{CHCl}_3$ @ 7.24 ppm), 3.60 (m, 1 H), 3.30 (m, 1 H), 2.35 (d, 1 H, J = 4), 2.16 (m, 1 H), 2.02 (m, 1 H), 1.71 (m, 2 H), 1.56 (m, 1 H), 1.27 (m, 3 H).

3. Discussion

This method of preparation of trans-isocyanocyclohexanol is a version of our literature procedure.² It represents a general procedure which gives comparable yields with a wide variety of epoxides.² The method described is a new approach to the synthesis of isocyanides. Traditionally, isocyanides have been prepared by dehydration of formamides, the reaction of dihalocarbenes with primary amines, and the reaction of active halides and olefins with cyanides.³⁻⁵

Isocyanides are useful intermediates because of their diverse reactivity.⁴ The β -hydroxy isocyanides which are prepared readily by our general procedure are particularly useful because of their straightforward conversion to β -amino alcohols in acids, and their catalyzed cyclization to oxazolines.²

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

trans-2-Isocyanocyclohexanol: Cyclohexanol, 2-isocyanato-, trans- (10);
(83152-97-0)

[(trans-2-Isocyanocyclohexyl)oxy]trimethylsilane: Silane, [(2-isocyano-
cyclohexyl)oxy]trimethyl-, trans- (10); (83152-87-8)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl- (8,9); (7677-24-9)

Zinc iodide (8,9); (10139-47-6)

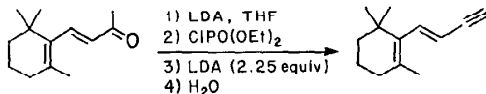
Cyclohexene oxide: 7-Oxabicyclo[4.1.0]heptane (8,9); (286-20-4)

Potassium fluoride (8,9); (7789-23-3)

CONVERSION OF METHYL KETONES INTO TERMINAL ALKYNES.

(E)-BUTEN-3-YNYL-2,6,6-TRIMETHYL-1-CYCLOHEXENE

(Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (E)-)



Submitted by Ei-ichi Negishi, Anthony O. King, and James M. Tour.¹

Checked by Weyton W. Tam and Robert V. Stevens.

1. Procedure

An oven-dried, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen and charged with 100 mL of tetrahydrofuran (THF) (Note 1). To this are added sequentially at 0°C, diisopropylamine (Note 2) (10.6 g, 14.7 mL, 105 mmol) and butyllithium in hexane (Note 3) (2.22 M, 47.3 mL, 105 mmol). The reaction mixture is stirred for 30 min and cooled to -78°C. β -Ionone (Note 4) (19.2 g, 20.3 mL, 100 mmol) is slowly added. After stirring the mixture for 1 hr at -78°C, diethyl chlorophosphate (Note 5) (18.1 g, 15.2 mL, 105 mmol) is added, and the reaction mixture is allowed to warm to room temperature over 2-3 hr (Reaction mixture A) (Note 6).

Lithium diisopropylamide is prepared in a separate 1-L flask from diisopropylamine (22.8 g, 31.6 mL, 225 mmol), butyllithium in hexane (2.22 M,

101 mL, 225 mmol), and THF (200 mL), as described above. To this is added over ca. 45 min at -78°C Reaction mixture A prepared above via a 16-G double-ended needle under a slight pressure of nitrogen. The resulting mixture is allowed to warm to room temperature over 2-3 hr, and is quenched with water (200 mL) at 0°C . The organic layer is separated, and the aqueous layer is extracted with pentane (3 x 50 mL). The combined organic layer is treated with ice-cold hydrochloric acid (1 N, 200 mL), water (2 x 100 mL), and saturated aqueous sodium bicarbonate (100 mL) to pH ≥ 8 (Note 7). After drying over magnesium sulfate, the volatile compounds are evaporated using a rotary evaporator at ca. 20 mm. The residue is distilled at 0.7 mm to provide (E)-buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene (Note 8) in one fraction boiling at $69-73^{\circ}\text{C}$ (0.7 mm) (Note 9). The yield by isolation has ranged from 12.5 g (72%) to 14.8 g (85%) (Note 10). The purity of the product by GLC is 98%.

2. Notes

1. Tetrahydrofuran available from Aldrich Chemical Company, Inc. was purified by distillation from sodium and benzophenone.
2. The submitters used diisopropylamine (99%) available from Aldrich Chemical Company, Inc. without further purification.
3. The submitters used butyllithium in hexane available from Alfa Products, Morton/Thiokol Inc.
4. The submitters used 98% pure β -ionone available from Aldrich Chemical Company, Inc. without further purification.
5. The submitters used diethyl chlorophosphate available from Aldrich Chemical Company.

6. Reduced yields of product were obtained by the checkers when reaction time at room temperature was reduced from 2-3 hr to 1 1/2 hr.

7. After extraction with hydrochloric acid, the pentane layer, upon addition of 100 mL of water, formed a poorly separating emulsion. Checkers found that, by addition of 100 mL of saturated aqueous sodium bicarbonate to this pentane-water emulsion, two easily separable layers can be formed.

8. The distilled product was found to be slightly yellow, and deepened to orange at room temperature. Storage at -5°C maintained the initial coloration for several weeks.

9. The product displays the following data: n_D^{24} 1.5130; IR (neat) cm^{-1} : 3300 (s), 2920 (s), 2080 (m), 1770 (w), 1630 (w), 1600 (w), 1455 (s), 1380 (m), 1355 (m), 1200 (m), 1030 (m), 960 (s); ^1H NMR (CDCl_3 , TMS) δ : 1.01 (s, 6 H), 1.2-1.8 (m with a singlet at 1.71, 7 H), 1.85-2.15 (m, 2 H), 2.90 (d, 1 H, $J = 2$), 5.42 (dd, 1 H, $J = 17$ and 2), 6.67 (d, 1 H, $J = 17$); ^{13}C NMR (CDCl_3 , TMS) δ : 19.17, 21.48, 28.75, 33.07, 33.98, 39.59, 77.29, 83.10, 111.36, 131.38, 136.90, 142.33 ppm.

10. The GLC trace (SE-30) of the reaction mixture shows essentially one peak (>98%) in the product region. In separate 5-20 mmol scale experiments, the GLC yields observed by using a paraffin internal standard were 90-95%.

3. Discussion

This procedure is based on a study of conversion of methyl ketones into terminal alkynes.² The scope of the procedure may be indicated by the results summarized in Table I.

TABLE I

CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES VIA ENOL PHOSPHATES

Ketone	Base ^a	<u>Yield of Acetylene, %</u>	
		GLC	Isolated
β -Ionone	LDA	95	85
Dihydro- β -ionone	LDA	90	85
Acetophenone	LDA	85	80
Pinacolone	LDA	90	78
Cyclohexyl methyl ketone	LDA	85	80
2-Octanone	LDA	23	--
2-Octanone	LTMP	75	--
6-Methyl-5-hepten-2-one	LDA	25	--
6-Methyl-5-hepten-2-one	LTMP	75	61

^aLDA = lithium diisopropylamide. LTMP = lithium 2,2,6,6-tetramethylpiperidide.

As can be seen in the Table, lithium diisopropylamide (LDA) is a satisfactory base in cases where the carbon group (R) of a methyl ketone (RCOCH_3) either is bulky or does not contain an α -methylene or α -methine group. In the other cases, LDA is relatively ineffective. In such cases, however, the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in place of LDA gives satisfactory results. The LTMP procedure appears to be the only documented method that is satisfactory for the conversion of the above-mentioned type.

The submitters have attempted the conversion of β -ionone into the desired dienyne by various known methods. In general, those involving acidic reagents or reaction conditions yielded the desired product in low yields (<50%) along with by-products, such as isomeric allenes, that appear near the product on GLC traces (SE-30). Such procedures include (a) PCl_5 in benzene, then NaNH_2 in NH_3 ,³ (b) PCl_5 and 2,6-lutidine, then NaNH_2 in NH_3 ,⁴ (c) POCl_3 in DMF, then NaOH ,⁵ and (d) $(\text{CF}_3\text{SO}_2)_2\text{O}$, CCl_4 , pyridine, then heat.⁶ Also unsatisfactory in the hands of submitters was a method involving the use of hydrazine in triethylamine, then iodine and triethylamine in THF, then methanolic potassium hydroxide.⁷ A procedure involving the use of sodium ethoxide, then diethyl chlorophosphate, and finally NaNH_2 in NH_3 ,⁸ on the other hand, converted β -ionone into the desired dienyne in <73% GLC yield. The procedure reported here may be viewed as a modification of the above method.

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Appendix

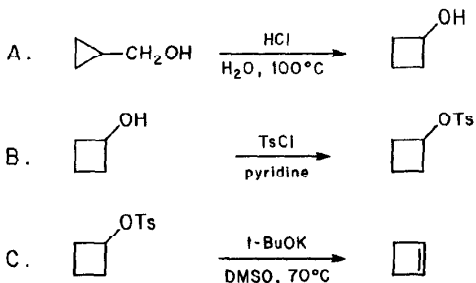
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(E)-Buten-3-ynyl-2,6,6-trimethyl-1-cyclohexene: Cyclohexene, 2-(1-buten-3-ynyl)-1,3,3-trimethyl-, (E)- (10); (73395-75-2)

β -Ionone: 3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (8,9); (14901-07-6)

Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester (8,9); (814-49-3)

CYCLOBUTENE



Submitted by J. Salaün and A. Fadel.¹

Checked by Lawrence R. McGee and Bruce E. Smart.

1. Procedure

A. Cyclobutanol. A 1-L, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar is charged with 600 mL of water, 57.5 mL (ca. 0.68 mol) of concentrated hydrochloric acid, and 57.7 g (0.80 mol) of cyclopropylcarbinol (Note 1). The reaction mixture is stirred and refluxed for 3 hr. Cyclobutanol is only partially soluble in water and soon separates. The reaction mixture is allowed to cool to room temperature and the flask is then immersed in an ice bath. To the cold, stirred mixture is added 24 g (0.6 mol) of sodium hydroxide pellets, followed by 6.7 g (0.08 mol) of sodium bicarbonate to complete the neutralization. The mixture is saturated with sodium chloride and extracted for 30 hr with diethyl ether using a liquid-liquid continuous extraction apparatus. The ethereal extract

is dried over anhydrous sodium sulfate and the drying agent is removed by filtration. The bulk of the solvent is distilled from the filtrate to give 55.0 g of residual liquid containing 88% cyclobutanol and 12% 3-buten-1-ol by gas chromatography (Note 2). The crude product is carefully distilled through spinning band columns to give 32.8 g (57%) of cyclobutanol, bp 122-124°C. Gas chromatographic analysis of the product shows it to be 95% pure (Notes 2,3,4).

B. Cyclobutyl tosylate. A 500-mL, three-necked, round-bottomed flask fitted with a stirrer and a thermometer is charged with 200 mL of pyridine (Note 5) and 32.3 g (0.448 mol) of cyclobutanol. The solution is stirred and chilled to 0°C, and then 89.8 g (0.471 mol) of p-toluenesulfonyl chloride (Note 6) is added in portions over a 20-min period. The reaction mixture is allowed to warm to room temperature and is stirred for 16 hr. The mixture is recooled to 0°C, and poured into 260 mL of concentrated hydrochloric acid in 800 mL of ice water. The mixture is extracted with three 300-mL portions of ether and the combined ethereal extracts are dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residue is held under high vacuum (0.03 mm) at room temperature for 3 hr to give 93.3 g (92%) of cyclobutyl tosylate as a pale yellow oil (Note 7).

C. Cyclobutene. A 500-mL, two-necked, round-bottomed flask is fitted with a 100-mL dropping funnel equipped with an argon-inlet tube, a magnetic stirring bar, and a water-cooled condenser. The outlet of the condenser is attached to an all glass transfer manifold. Two weighed traps fitted with gas-tight stopcocks and immersed in dry ice/acetone baths are attached to the manifold. A calcium chloride drying tube is attached to the exit of the second trap. While the system is continuously purged with a slow stream of argon, the flask is charged with 33.6 g (0.30 mol) of potassium tert-butoxide

and 120 mL of anhydrous dimethyl sulfoxide (Note 8), and a solution of 25.6 g (0.113 mol) of cyclobutyl tosylate in 30 mL of anhydrous dimethyl sulfoxide is placed in the dropping funnel. The potassium tert-butoxide suspension is stirred vigorously and heated to 70°C. The cyclobutyl tosylate solution is then added dropwise over a period of 10 min (Note 9). After the addition is completed, the reaction mixture is stirred at 70°C for an additional 2 hr. The manifold system is closed off from the reaction vessel and the material collected in the first trap is slowly warmed. The product distills at ca. 2°C into the second dry ice-cooled trap to give 4.3-5.1 g (70-84%) of cyclobutene [lit.² bp 2°C] (Notes 10 and 11).

2. Notes

1. The checkers obtained cyclopropylcarbinol from the Aldrich Chemical Company, Inc. It can be readily prepared by the reduction of cyclopropanecarboxylic acid with lithium aluminum hydride.³

2. A 25-m x 0.3-mm HP Ultra Silicone capillary column at 70°C with 30 psi helium head pressure was used for the chromatographic analysis: retention times of 3-buten-1-ol and cyclobutanol are 1.19 min and 1.35 min, respectively. The submitters used a 3-m x 0.3-cm 20 M Carbowax column at 90°C/8 psi hydrogen and they reported retention times of 13 min and 20 min for 3-buten-1-ol and cyclobutanol, respectively.

3. The crude product was first distilled on a 50-cm x 0.8-cm spinning band column (reflux ratio 10:1) to give 19.6 g of cyclobutanol, bp 124°C. The forerun fractions, bp 66-123°C (23.0 g), were combined and redistilled on a 30-cm x 0.8 cm spinning band column (reflux ratio 25:1) to give an additional 13.2 g of cyclobutanol, bp 122-123°C. The major by-product, 3-buten-1-ol,

boils at 112-114°C. Gas chromatographic analysis of the combined product fractions indicates a mixture of 95% cyclobutanol/3-buten-1-ol (99.7%/0.3%) and 5% unidentified compounds.

4. Cyclobutanol shows the following ^1H NMR spectrum (CDCl_3) δ : 4.54 (s, 1 H, OH), 4.16 (pentet, 1 H, $J = 7.5$), 1.1-2.4 (m, 6 H).

5. The pyridine was distilled from calcium hydride and stored over potassium hydroxide.

6. The p-toluenesulfonyl chloride was obtained from the Aldrich Chemical Company, Inc., and was recrystallized from hexane prior to use.

7. The product is >99% pure by NMR and shows the following spectrum: ^1H NMR (CDCl_3) δ : 7.79 (d, 2 H, $J = 9.0$), 7.32 (d, 2 H, $J = 9.0$), 4.77 (quintet, 1 H, $J = 7.5$), 2.47 (s, 3 H), 1.1-2.3 (m, 6 H).

8. Potassium tert-butoxide was obtained from the Aldrich Chemical Company, Inc. The dimethyl sulfoxide was distilled from calcium hydride and stored under argon.

9. The reaction mixture turns green, then blue indigo, and finally dark pink during the addition.

10. The submitters report obtaining 5.2 g of 99.2% pure cyclobutene. The product obtained by the checkers was pure by NMR spectroscopy and it shows the following ^1H NMR spectrum (CDCl_3) δ : 2.55 (s, 4 H), 6.00 (s, 2 H).

11. The cyclobutene can be converted to 1,2-dibromocyclobutane by distilling 4.3-7.3 g (0.079-0.135 mol) of cyclobutene into 100 mL of pentane chilled to -40°C, followed by adding a solution of 15.5-32.0 g (0.097-0.200 mol) of bromine in 30 mL of pentane. After the usual work-up with aqueous sodium thiosulfate and distillation, 14.3-25.3 g (84-87.5%) of pure 1,2-dibromocyclobutane, bp 60°C (6 mm), is obtained. It shows the following ^1H NMR spectrum (CDCl_3) δ : 1.90-3.03 (m, 4 H), 4.27-4.70 (m, 2 H). The 1,2-

dibromocyclobutane can be conveniently converted back to cyclobutene by debromination with zinc in ethanol.⁴

3. Discussion

Cyclobutene has been prepared (1) by pyrolysis of cyclobutyldimethylamine oxide⁴⁻⁶ and cyclobutyltrimethylammonium hydroxide^{4,6,7} (50-73% yield), which were prepared in eight steps from malonate esters (2.0-2.1% overall yield of cyclobutene contaminated with 1,3-butadiene), (2) by pyrolysis of the products of cycloaddition of dimethyl acetylenedicarboxylate with cyclooctatriene⁸⁻¹⁰ (30-32% overall yield) or with cyclooctatetraene¹¹⁻¹³ (34-39% overall yield), (3) by photolysis of butadiene leading to cyclobutene (30% yield) and bicyclo[1.1.0]butane (5% yield),^{14,15} (4) by oxidation of cyclobutylcarboxylic acid¹⁶ with lead tetraacetate¹⁷ (67% yield) (11.8% overall yield), (5) by fragmentation of 1,2-cyclobutyl thiocarbonate with trialkyl phosphite¹⁸ (68% yield based on cis-1,2-dihydroxycyclobutane), (6) by ring expansion of cyclopropylcarbene¹⁹ (7) from cyclobutylidene²⁰ and (8) by base induced ring-expansion of cyclopropylmethyl tosylate with potassium tert-butoxide in dimethyl sulfoxide leading to a 1:1 mixture of cyclobutene and methylenecyclopropane.²¹ None of these methods appears to be practical.

The present procedure offers in good yields a simple and ready preparation of pure cyclobutene from the easily available cyclopropylcarbinol. The product is free of the impurities (e.g., 1,3-butadiene, bicyclobutane, methylenecyclopropane) usually obtained with the various methods so far reported. The procedure described for the synthesis of cyclobutanol is patterned after the acid-catalyzed rearrangement of cyclopropylcarbinol reported by Roberts²² and Roček.²³

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclobutene (8,9); (822-35-5)

Cyclobutanol (8,9); (2919-23-5)

Cyclopropylcarbinol: Cyclopropanemethanol (8,9); (2516-33-8)

Cyclobutyl tosylate: Cyclobutanol, p-toluenesulfonate (8); Cyclobutanol, 4-methylbenzenesulfonate (9); (10437-85-1)

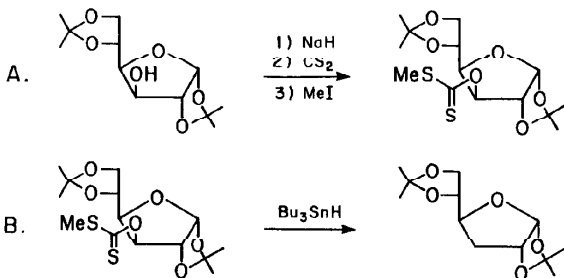
p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

Potassium tert-butoxide: tert-Butyl alcohol, potassium salt (8); 2-Propanol, 2-methyl-, potassium salt (9); (865-47-4)

DEOXYGENATION OF SECONDARY ALCOHOLS:

3-DEOXY-1,2:5,6-DI-O-ISOPROPYLIDENE- α -D-ribo-HEXOFURANOSE

(α -D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)-)



Submitted by S. Iacono and James R. Rasmussen.¹

Checked by Peter J. Card and Bruce E. Smart.

1. Procedure

Caution! Carbon disulfide, iodomethane and tributyltin hydride are poisonous and should be handled in a well-ventilated hood.

A. *1,2:5,6-Di-O-isopropylidene-3-O-(S-methyl dithiocarbonate)- α -D-glucofuranose.* A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet adapter, pressure-equalizing addition funnel, and a stopper is charged with 26.0 g (0.10 mol) of 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose, 25 mg of imidazole (Note 1), and 400 mL of anhydrous tetrahydrofuran (Note 2). The reaction vessel is flushed with

nitrogen and a nitrogen atmosphere is maintained during the ensuing steps. Over a 5-min period, 7.2 g (0.150 mol) of a 50% sodium hydride dispersion (Note 3) is added. Vigorous gas evolution is observed. After the reaction mixture is stirred for 20 min, 22.8 g (0.30 mol) of carbon disulfide is added all at once. Stirring is continued for 30 min, after which time 25.3 g (0.177 mol) of iodomethane is added in a single portion. The reaction mixture is stirred another 15 min, and 5.0 mL of glacial acetic acid is added dropwise to destroy excess sodium hydride. The solution is filtered (Note 4) and the filtrate is concentrated on a rotary evaporator. The semi-solid residue is extracted with three 100-mL portions of ether and the combined ether extracts are washed with two 100-mL portions of saturated sodium bicarbonate solution and two 100-mL portions of water. The ethereal solution is dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed by rotary evaporation. The product is dried further at 0.05 mm overnight. The resulting orange syrup is distilled (Kugelrohr) to give 32.2-33.0 g (92-94%) of product, bp 153-160°C (0.5-1.0 mm) (Note 5).

B. 3-Deoxy-1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranose. A dry, 1-L, round-bottomed flask is equipped with a magnetic stirring bar, and a reflux condenser to which a nitrogen inlet is attached. The apparatus is charged with 500 mL of anhydrous toluene (Note 6), 24.7 g (0.085 mol) of tributyltin hydride (Note 7) and 19.25 g (0.055 mol) of 1,2:5,6-di-O-isopropylidene-3-O-(S-methyl dithiocarbonate)- α -D-glucufuranose. The reaction mixture is heated at reflux under a nitrogen atmosphere until TLC analysis indicates the disappearance of starting materials (4-7 hr) (Note 8). During this time the reaction solution changes from deep yellow to nearly colorless. The toluene is removed on a rotary evaporator to yield a thick, oily residue that is

partitioned between 250-mL portions of petroleum ether and acetonitrile. The acetonitrile layer is separated and washed with three 100-mL portions of petroleum ether and is then concentrated on a rotary evaporator. The residual yellow oil is taken up in hexane/ethyl acetate (10:1) and filtered through a pad of silica gel (Note 9). The filtrate is concentrated and the residual oil is distilled to give 10.0 g (75%) of product as a colorless syrup, bp 72-73°C (0.2 mm); n_D^{25} 1.4474 (Note 10).

2. Notes

1. 1,2:5,6-Di-O-isopropylidene- α -D-glucofuranose and imidazole were purchased from Aldrich Chemical Company, Inc., and used without further purification. Alternatively, the glucofuranose starting material can be prepared by standard methods from D-glucose.²

2. Reagent-grade tetrahydrofuran was freshly distilled from a purple solution of sodium and benzophenone.

3. Sodium hydride, a 50% dispersion in mineral oil, was purchased from Alfa Products, Morton/Thiokol Inc. It is not necessary to remove the mineral oil before conducting the reaction.

4. The collected salts should be disposed of carefully by first rinsing with isopropyl alcohol to ensure that no sodium hydride remains.

5. The submitters report pure product with bp 135-136°C (0.07 mm). The material obtained by the checkers is pure by NMR analysis. It shows ^1H NMR (CDCl_3) δ : 1.35 (s, 6 H), 1.42 (s, 3 H), 1.55 (s, 3 H), 2.60 (s, 3 H), 3.90-4.40 (m, 4 H), 4.68 (d, 1 H), 5.85-6.0 (m, 2 H).

6. Reagent-grade toluene was dried by distilling the toluene-water azeotrope and then cooling the remaining liquid under an atmosphere of nitrogen.

7. Tributyltin hydride was purchased from Aldrich Chemical Company, Inc. and stored under nitrogen at 4°C.

8. An E. Merck Silica Gel 60 F-254 0.25-mm plate was used for the TLC analysis.

9. Silica Woelm TSC, obtained from Woelm Pharma, was used.

10. The product is pure by NMR and TLC analyses and shows ^1H NMR (CDCl_3) δ : 1.27 (s, 3 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.60-1.90 (m, 1 H), 2.05-2.30 (dd, 1 H), 3.65-4.25 (m, 4 H), 4.71 (t, 1 H), 5.77 d, 1 H).

3. Discussion

This procedure illustrates a simple, general method for the deoxygenation of secondary hydroxyl groups. It is particularly useful for reducing hindered alcohols. The method was first described by Barton and McCombie³ who have reviewed a number of other examples.⁴

A variety of thiocarbonyl derivatives, in addition to xanthate esters, undergo reductive homolytic cleavage when treated with tributyltin hydride. These include thiobenzoates,³ thiocarbonylimidazolides,^{3,5} and phenyl thionocarbonate esters.⁶ The S-methyl xanthate ester is a particularly convenient intermediate to prepare because of its ease of formation and the low cost of the reagents. Its use is precluded, however, by the presence of base-labile protecting groups and, in such cases, the thiocarbonylimidazolidine or phenyl thionocarbonate ester will generally prove satisfactory. Additional methods for the radical deoxygenation of alcohols are described in a review by Hartwig.⁷

The tributyltin hydride reduction usually proceeds without complications. The most common byproduct is starting alcohol, which is postulated to be derived from a mixed thioacetal.³ Use of the phenyl thionocarbonate ester has been reported to minimize this side reaction in cases where it is a problem.⁶

3-Deoxy-1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranose has been prepared by a variety of other methods, the most widely used of which is the Raney nickel reduction of the 3-S-[(methylthio)carbonyl]-3-thioglucofuranose derivative.⁸

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Deoxy-1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranose: D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-di-O-isopropylidene, α - (8); α -D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)- (9); (4613-62-1)

1,2:5,6-Di-O-isopropylidene- α -D-glucofuranose: Glucofuranose, 1,2:5,6-di-O-isopropylidene, α -D- (8); α -D-glucofuranose, 1,2:5,6-bis-O-(1-methylethylidene)- (9); (582-52-5)

1,2:5,6-Di-O-isopropylidene-3-O-(S-methyl dithiocarbonate)- α -D-glucofuranose: Glucofuranose, 1,2:5,6-di-O-isopropylidene-, S-methyl dithiocarbonate, α -D- (8,9); (16667-96-2)

Imidazole (8): 1 H-Imidazole (9); (288-32-4)

Sodium hydride (8,9); (7646-69-7)

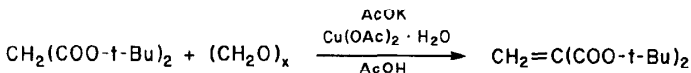
Carbon disulfide (8,9); (75-15-0)

Iodomethane: Methane, iodo- (8,9); (74-88-4)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

DI-tert-BUTYL METHYLENEMALONATE

(Propanedioic acid, methylene-, bis(1,1-dimethylethyl)ester)



Submitted by Paloma Ballesteros and Bryan W. Roberts.¹

Checked by Doreen L. Weller and James D. White.

1. Procedure

Caution! This reaction should be carried out in an efficient hood to prevent exposure to formaldehyde and acetic acid.

A 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a reflux condenser protected by a calcium chloride drying tube. Into the flask are placed 30.0 g (0.14 mol) of di-tert-butyl malonate (Note 1), 8.4 g (0.28 mol) of paraformaldehyde (Note 2), 1.4 g (0.014 mol) of potassium acetate, 1.4 g (0.007 mol) of cupric acetate monohydrate, and 70 mL of glacial acetic acid. The resulting green-white suspension is placed in an oil bath preheated to 90–100°C and stirred for 2 hr (Note 3). The reaction mixture is allowed to cool to room temperature, and the reflux condenser is replaced with a short-path distillation apparatus, the vacuum outlet of which is connected in sequence to a trap cooled in acetone-dry ice, a potassium hydroxide trap, another trap cooled in acetone-dry ice, and a vacuum pump. The receiving flask is cooled in acetone-dry ice, and the system is evacuated over approximately 1 hr to remove acetic acid and other volatile material

(Note 4). The bath temperature is increased to 40-50°C for 15 min and then is rapidly raised to 140-150°C to drive over crude product, which is collected over a boiling point range of 60-82°C (Note 5). When distillate ceases to come over, the bath temperature is increased to 170°C and distillate is collected over the same boiling point range until the reaction mixture turns from blue to green-brown. The total amount of crude product collected is 24.3 g. This material is dissolved in 50 mL of ether and washed with saturated aqueous sodium bicarbonate solution (4 x 20 mL) and water (25 mL). The combined aqueous fractions are extracted with 50 mL of ether, and the combined ether extracts are dried over magnesium sulfate for 10 min (Note 6). Filtration and evaporation on a rotary evaporator give 20.0 g of crude product which is distilled through an 8-cm Vigreux column. The di-tert-butyl methylenemalonate is collected at 60-67°C/0.1 mm and weighs 15.3 g (48%) (Note 7). The product is somewhat unstable and should be stored in Pyrex in the refrigerator.

2. Notes

1. Di-tert-butyl malonate was prepared according to the procedure of Johnson; see *Org. Synth., Collect. Vol. IV 1963*, 261.

2. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc., and stored in a desiccator over phosphorus pentoxide.

3. After approximately 25 min, the suspension dissolves and the reaction mixture becomes blue-green.

4. At the beginning of the evaporation, the pressure is controlled to minimize bumping of the vigorously boiling mixture.

5. During this operation the pressure varies between 0.3 and 1.5 mm. As the temperature is raised, the reaction mixture turns blue and gas evolution is observed.

6. The procedure can be interrupted at this point and the ether extracts dried over magnesium sulfate overnight in the refrigerator.

7. The bath temperature should not exceed 100°C in order to prevent contamination of the product with the bis(hydroxymethyl) derivative of di-tert-butyl malonate. The product exhibits single peaks in the ^1H NMR spectrum (CDCl_3 , 250 MHz) at 1.51 and 6.25 ppm and contains approximately 6% of di-tert-butylmalonate as indicated by a peak at 1.47 ppm. Contamination by the bis(hydroxymethyl) derivative is indicated by a peak at 1.48 ppm.

3. Discussion

Methylenemalonate esters are potentially useful activated alkenes which can serve as electrophilic partners in the Michael and cycloaddition reactions and, in the process, introduce a gem-diester functionality for further synthetic transformation. The simple esters, however, have a marked propensity toward spontaneous polymerization and, as a consequence, have been used only sparingly in the Michael reaction,² the Diels-Alder reaction,³ [2 + 2] cycloaddition,⁴ and [3 + 2] cycloaddition.⁵ The recently prepared di-tert-butyl analog⁶ is advantageous in being longer lived and suitable for conventional synthetic operations, and in introducing a readily cleaved diester moiety. In its most useful application thus far, the compound has been found to react under mild conditions with enamines with no added catalyst or with enol ethers and acetates under Lewis acid catalysis to give either cyclobutanes or Michael adducts, depending upon alkene structure.⁷

Di-tert-butyl methylenemalonate was originally prepared by phenylsulfenylation of di-tert-butyl methylmalonate and thermal elimination of the related sulfoxide.⁶ Because methylenemalonate esters are customarily prepared by Knoevenagel-type condensation of malonic esters with formaldehyde equivalents, the considerably more convenient procedure described herein was subsequently adapted from Bachman and Tanner's study using paraformaldehyde under metal ion catalysis.^{3a} The approximately 6% di-tert-butyl malonate accompanying the product has presented no interference in the aforementioned reactions with nucleophilic alkenes under neutral or acidic conditions, but its presence should be taken into consideration in other applications.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Di-tert-butyl methylenemalonate: Propanedioic acid, methylene-, bis(1,1-dimethylethyl) ester (11); (86633-09-2)

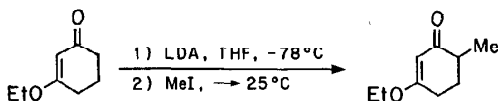
Di-tert-butyl malonate: Propanedioic acid, bis(1,1-dimethylethyl) ester (9); (541-16-2)

Paraformaldehyde: Poly(oxymethylene) (8,9); (9002-81-7)

THE STORK-DANHEISER KINETIC ALKYLATION PROCEDURE.

SYNTHESIS OF 3-ETHOXY-6-METHYL-2-CYCLOHEXEN-1-ONE

(2-Cyclohexen-1-one, 3-ethoxy-6-methyl-)



Submitted by Andrew S. Kende and Pawel Fludzinski.¹

Checked by P. Wovkulich, F. Barcelos and Gabriel Saucy.

1. Procedure

A dry, 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirrer, and two 500-mL pressure-equalizing dropping funnels. One of the dropping funnels is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 400 mL of anhydrous tetrahydrofuran (Note 2) and 51.6 g (71.5 mL, 0.51 mol) of anhydrous diisopropylamine (Note 3). The flask is cooled to 0° with an ice bath. A 1.7-M hexane solution of butyllithium (288 mL, 0.49 mol) is added dropwise with stirring over a 30-min period. The resulting lithium diisopropylamide is cooled to -78°C with a dry ice-acetone bath (Note 4). A solution of 53.9 g (0.385 mol) of 3-ethoxy-2-cyclohexen-1-one (Note 5) in 250 mL of anhydrous tetrahydrofuran is added dropwise with stirring at -78°C over a 1-hr period. The solution is stirred at -78°C for 30 min followed by the rapid addition of 114 g (50 mL, 0.80 mol) of methyl iodide (Note 6). After 5 min, the cooling

bath is removed, the mixture is allowed to warm to room temperature, and is stirred overnight. The reaction is quenched with 300 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 75 mL of diethyl ether. The organic phases are combined and washed twice with 150 mL of water, once with 150 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by distillation at reduced pressure affords 54-55 g (91-93%) of 3-ethoxy-6-methyl-2-cyclohexen-1-one as a colorless oil, bp 131-133°C (15 mm) (Notes 7, 8).

2. Notes

1. This is accomplished by alternately evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.

2. Tetrahydrofuran is freshly distilled from sodium and benzophenone.

3. Diisopropylamine is distilled from calcium hydride.

4. The flask is cooled with the dry ice-acetone bath for 1 hr before the next addition to insure complete cooling of the solution.

5. *Organic Synth., Coll. Vol. V 1973*, 539.

6. Methyl iodide was obtained from Eastman Organic Chemicals and used directly from a fresh bottle.

7. Spectroscopic data for 3-ethoxy-6-methyl-2-cyclohexen-1-one are as follows: ^1H NMR (CDCl_3) δ : 1.16 (d, 3 H, $J = 7$), 1.36 (t, 3 H, $J = 6$), 1.6-2.6 (m, 5 H), 3.92 (q, 2 H, $J = 6$), 5.32 (s, 1 H); IR (neat, cm^{-1}): 1670, 1600.

8. In the procedure as originally submitted, the authors used 1 equiv of base and distilled the product through a short path distillation apparatus with 75-80% yields. The checkers used excess lithium diisopropylamide (suggested by Professor Clayton Heathcock) as specified in this procedure, and distilled the product through a 15-cm Vigreux column to afford 1.7-1.9 g of forerun (97-98.5% pure by GC) and 54.1-55.3 g (91.4-93.4% yield) of main fraction. The short path distillation is probably quite adequate.

3. Discussion

The Stork-Danheiser² alkylation of 3-alkoxy-2-cyclohexenones under conditions of kinetic enolate formation at the 6-position has enjoyed extensive application in alicyclic synthesis. Such kinetic enolates have served as nucleophiles for a number of alkylations,³⁻²⁴ aldol condensations,²⁵⁻²⁷ and Michael additions.^{28,29} Reductive transposition of the resulting products to 4-substituted cyclohexenones has likewise found synthetic application.³⁰⁻³³

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Ethoxy-6-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-ethoxy-6-methyl- (10); (62952-33-4)

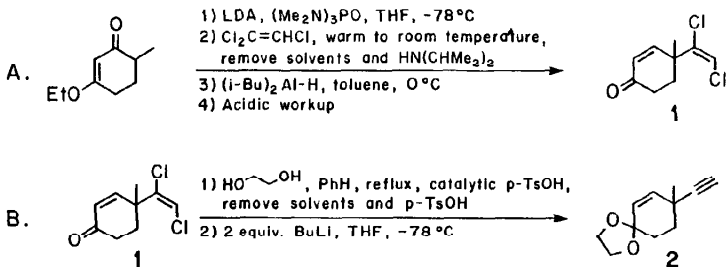
Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

3-Ethoxy-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-ethoxy- (8,9); (5323-87-5)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

**DICHLOROVINYLATION OF AN ENOLATE. SYNTHESIS OF
8-ETHYNYL-8-METHYL-1,4-DIOXASPIRO[4.5]DEC-6-ENE
(1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl-)**



Submitted by Andrew S. Kende and Pawel Fludzinski.¹

Checked by P. Wovkulich, F. Barcelos and Gabriel Saucy.

1. Procedure

Caution! Hexamethylphosphoric triamide and trichloroethylene are cancer-suspect agents. All operations with either one should be performed in an efficient hood. The use of disposable gloves is highly recommended. Glassware should be rinsed with copious amounts of water into separate waste containers before removal from the hood.

A. 4-(E-1,2-Dichlorovinyl)-4-methyl-2-cyclohexen-1-one (1). A dry, 3-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted

with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 1500 mL of anhydrous tetrahydrofuran (Note 2) and 38.9 g (54 mL, 0.38 mol) of diisopropylamine (Note 3). The flask is cooled to 0°C with an ice bath. A 1.51-M hexane solution of butyllithium (255 mL, 0.38 mol) is added dropwise with stirring over a 30 min period. The resulting lithium diisopropylamide is cooled to -78°C with a dry ice-acetone bath (Note 4). A solution of 57.8 g (0.38 mol) of 3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 5) in 400 mL of anhydrous tetrahydrofuran is added dropwise with stirring at -78°C over a 90-min period, followed immediately by the addition of 68 g (66 mL, 0.38 mol) of neat hexamethylphosphoric triamide (Note 6) over a 5-min period. The solution is stirred at -78°C for 45 min, followed by the dropwise addition of 52.6 g (36 mL, 0.40 mol) of neat trichloroethylene (Note 7). The solution is allowed to warm to room temperature slowly over a 6-hr period. As the solution warms, the color changes from pale yellow to olive green, to pale red, and finally to black. After 6 hr (Note 8) the solution is quenched with 1000 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 250 mL of diethyl ether. The organic phases are combined and washed four times with 750 mL of water, twice with 750 mL of brine, and dried over magnesium sulfate. The solvent is removed on a rotary evaporator and recovered starting material is removed by fractional distillation at 91-93°C (1 mm) through a 15-cm Vigreux column. The residual crude 6-(E-1,2-dichlorovinyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 9) is dissolved in 400 mL of toluene and placed in a dry, 2-L, one-necked, round-bottomed flask, equipped with a mechanical stirrer; a 500-mL pressure-equalizing dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to 0°C with an ice bath.

A 1-M hexane solution of diisobutylaluminum hydride (400 mL, 0.40 mol) (Note 10) is added dropwise with stirring at 0°C over a 1-hr period. The solution is stirred for 2 additional hr at 0°C. To quench the reaction 200 mL of methanol is carefully added to the stirred reaction mixture, followed slowly at first then more rapidly with 400 mL of water and then 300 mL of 10% sulfuric acid solution. After the mixture is stirred for 10 min, it is transferred to a separatory funnel and 500 mL of 10% sulfuric acid solution is added. The separatory funnel is shaken vigorously for 5 min and the organic phase is separated. The aqueous phase is extracted four times with 300 mL of diethyl ether. The organic phases are combined and washed twice with 300 mL of saturated sodium bicarbonate solution, twice with 300 mL of water, twice with 300 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short path distillation at reduced pressure affords 31-34 g (40-44%, based on 3-ethoxy-6-methyl-2-cyclohexen-1-one) of 4-(E-1,2-dichlorovinyl)-4-methyl-2-cyclohexen-1-one (1) as a colorless oil, bp 75-78°C (0.1 mm) (Note 11).

B. *8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene* (2). A dry, 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap and a reflux condenser. The flask is charged with 500 mL of benzene, 12.0 g (0.059 mol) of 4-(E-1,2-dichlorovinyl)-4-methyl-2-cyclohexen-1-one, 12.2 g (11 mL, 0.20 mol) of ethylene glycol and 40 mg (a catalytic amount) of p-toluenesulfonic acid. After the solution is refluxed for 24 hr, it is poured into 200 mL of saturated sodium bicarbonate solution. The organic phase is separated and the aqueous phase is extracted four times with 50 mL of diethyl ether. The organic phases are combined and washed twice with 100 mL of water, once with 100 mL of brine, and dried over magnesium sulfate. The solvent is removed on a rotary evaporator, and the resulting

crude 8-(E-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene (Note 12) is dissolved in 200 mL of anhydrous tetrahydrofuran and placed in a dry, 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to -78°C with a dry ice-acetone bath (Note 4). A 1.51-M hexane solution of butyllithium (76 mL, 0.12 mol) is added dropwise with stirring at -78°C over a 30-min period. The solution is stirred at -78°C for 2 hr, the cold bath is removed, and stirring is continued for 90 min. The solution is poured into 100 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 25 mL of diethyl ether. The organic phases are combined and washed twice with 75 mL of water, twice with 75 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short path distillation at reduced pressure yields 5.5-6.3 g (52-60%) of 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene as a colorless oil, bp $88-90^{\circ}\text{C}$ (1 mm) (Note 13).

2. Notes

1. This is accomplished by alternately evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.

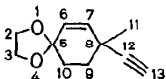
2. Tetrahydrofuran is freshly distilled from sodium and benzophenone, as is all tetrahydrofuran used in this procedure.

3. Diisopropylamine is distilled from calcium hydride.

4. The flask is cooled with the dry ice-acetone bath for 1 hr before the next addition to insure complete cooling of the solution.

5. See *Organic Syntheses*, this volume p. 68.
6. Hexamethylphosphoric triamide is freshly distilled from calcium hydride.
7. Trichloroethylene is freshly distilled from phosphorus pentoxide.
8. On a smaller scale, the reaction warms to room temperature more quickly and can be worked up after 4 hr. Extended reaction times (e.g., overnight) lead to the formation of by-products.
9. Distillation is not necessary at this point. Spectroscopic data for 6-(E-1,2-dichlorovinyl)-3-ethoxy-5-methyl-2-cyclonexen-1-one is as follows:
 ^1H NMR (CDCl_3) δ : 1.38 (t, 3 H, $J = 6$), 1.48 (s, 3 H), 1.8-2.7 (m, 4 H), 3.96 (q, 2 H, $J = 6$), 5.44 (s, 1 H), 6.36 (s, 1 H). A purified sample (bp 140-142°C, 1 mm) gave satisfactory analysis. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_2$: C, 53.02; H, 5.68. Found: C, 53.20; H, 5.43.
10. Diisobutylaluminum hydride was purchased from Aldrich Chemical Company, Inc. Since the reagent is not titrated, excess is used to insure complete reduction.
11. Spectroscopic data for 4-(E-1,2-dichlorovinyl)-4-methyl-2-cyclohexen-1-one are as follows: ^1H NMR (CDCl_3) δ : 1.50 (s, 3 H), 1.8-2.8 (m, 4 H), 5.92 (d, 1 H, $J = 10$), 6.34 (s, 1 H), 7.04 (d, 1 H, $J = 10$); ms (75 eV) m/e 204; IR (CHCl_3) cm^{-1} : 1680. Anal. Calcd $\text{C}_9\text{H}_{10}\text{Cl}_2\text{O}$: C, 52.71; H, 4.91. Found: C, 53.08, H, 5.03.
12. Spectroscopic data for 8-(E-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene is as follows: ^1H NMR (CDCl_3) δ : 1.36 (s, 3 H), 1.6-2.6 (m, 4 H), 3.88-4.08 (m, 4 H), 5.56 (d, 1 H, $J = 10$), 6.08 (d, 1 H, $J = 10$), 6.28 (s, 1 H).

13. Spectroscopic data for 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene are follows: ^1H NMR (CDCl_3) : 1.32 (s, 3 H), 1.6-2.2 (m, 4 H), 2.12 (s, 1 H), 3.88-4.04 (m, 4 H), 5.64 (AB q, 2 H, $J = 10$); ms (75 eV) m/e 178; IR (neat) cm^{-1} : 3290, 2100. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C, 74.13; H, 7.92. Found: C, 73.96; H, 7.78. ^{13}C NMR (CDCl_3) δ : 28.1 (C^{11}), 30.5 (C^9 or C^{10}), 31.4 (C^8), 34.6 (C^9 or C^{10}), 64.0 (C^2 or C^3), 64.3 (C^2 or C^3), 60.4 (C^{13}), 88.3 (C^{12}), 104.5 (C^5), 126.3 (C^6), 137.0 (C^7).



3. Discussion

Trichloroethylene serves as an effective reagent for the dichlorovinylolation of lithium enolates of several conjugated ketones. Under similar reaction conditions, 2,6-dimethylcyclo-2-hexen-1-one and 2-ethyl-5-methoxy-1-tetralone give the analogous dichlorovinyl adduct in comparable yield.² This procedure represents an heretofore unknown, uncatalyzed³ carbon-carbon bond forming reaction between enolates and a polychloroolefin which can subsequently provide access to α - and γ -acetylenic ketones.⁴

1. Department of Chemistry, University of Rochester, Rochester, NY 14627.
2. Kende, A. S.; Benecbie, M.; Curran, D. P.; Fludzinski, P.; Swenson, W.; Clardy, J. *Tetrahedron Lett.* **1978**, 4513.
3. For examples of Ni-catalyzed vinylation and arylation of enolates by bromides and iodides, see Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

4. The trichloroethylene condensation has been shown to proceed by way of dichloroacetylene as an obligatory intermediate in a carbanion chain mechanism. See: Kende, A. S.; Fludzinski, P. *Tetrahedron Lett.* **1982**, 23, 2369, 2373; Kende, A. S.; Fludzinski, P.; Hill, J. M.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, 106, 3551.

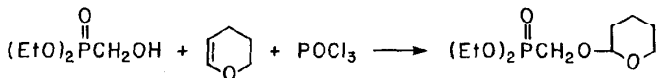
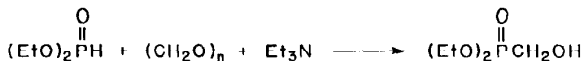
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene: 1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl (10); (73843-26-2)
- Hexamethylphosphoric triamide: Phosphoric triamide, hexamethyl- (8,9); (680-31-9)
- Trichloroethylene: Ethylene, trichloro- (8); Ethene, trichloro- (9); (79-01-6)
- 4-(E-1,2-Dichlorovinyl)-4-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 4-(1,2-dichloroethenyl)-4-methyl- (10); (73843-27-3)
- Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)
- Butyllithium: Lithium, butyl- (8,9); (109-72-8)
- 3-Ethoxy-6-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-ethoxy-6-methyl- (10); (62952-33-4)
- 6-(E-1,2-Dichlorovinyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 6-(1,2-dichloroethenyl)-3-ethoxy-6-methyl- (10); (73843-25-1)
- Diisobutylaluminum hydride: Aluminum, hydrodiisobutyl- (8); Aluminum, hydrobis(2-methylpropyl)- (9); (1191-15-7)
- Ethylene glycol: Ethylene glycol (8); 1,2-Dihydroxyethane (9); (107-21-1)

DIETHYL [(2-TETRAHYDROPYRANYLOXY)METHYL]PHOSPHONATE

(Phosphonic acid, [(tetrahydro-2H-pyran-2-yl)oxy]methyl-, diethyl ester)



Submitted by Arthur F. Kluge.¹

Checked by Ronaldo A. Pilli, Kenneth S. Kirshenbaum,

Clayton H. Heathcock, and K. Barry Sharpless.

1. Procedure

A. Diethyl hydroxymethylphosphonate. To a 250-mL, round-bottomed flask equipped with a magnetic stirring bar and an efficient reflux condenser are added 69 g (64.4 mL, 0.5 mol) of diethyl phosphite (Note 1), 15 g (0.5 mol) of paraformaldehyde, and 5.1 g (0.05 mol) of triethylamine. The mixture is placed in an oil bath preheated to 100–120°C. The temperature is increased to 120–130°C, and the mixture is stirred at this temperature for 4 hr. The stirring bar is removed, the flask is transferred to a rotary evaporator, and most of the triethylamine is removed by heating under reduced pressure of ca. 15 mm and with a bath temperature of ca. 80°C. Kugelrohr distillation at 125°C (0.05 mm) (Note 2) gives 41.4–54.9 g (49–65%) of material of sufficient purity for the next step (Notes 3 and 4).

B. Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate. A mixture of 33.63 g (0.2 mol) of diethyl hydroxymethylphosphonate, 21 g (0.25 mol) of dihydropyran, and 150 mL of diethyl ether is placed in a stoppered flask, and 20 drops of phosphorus oxychloride is added while the contents are swirled manually. After 3 hr at room temperature the reaction is monitored by TLC (Note 5). The mixture is diluted with diethyl ether, transferred into a separatory funnel, and shaken successively with 100 mL of saturated sodium bicarbonate solution, 100 mL of water, and 100 mL of saturated sodium chloride solution. The ether solution is dried over MgSO_4 , filtered, and the ether is removed with a rotary evaporator. Kugelrohr distillation of the residue (110°C, 0.05 mm) gives 42.4-46.9 g (84-93%) of material of sufficient purity for use in homologation reactions (Notes 6 and 7).

2. Notes

1. Diethyl phosphite, paraformaldehyde, and triethylamine were obtained from Aldrich Chemical Company, Inc. Dihydropyran was obtained from MC and D Manufacturing Chemists.

2. Attempted isolation of diethyl hydroxymethylphosphonate by standard vacuum distillation technique is accompanied by extensive decomposition. The use of Kugelrohr apparatus allows the isolation to be accomplished at a lower temperature, and therefore the product is obtained in higher yield. Alternately, the checkers found that distillation using a 2" wiped-film molecular still (Pope Scientific, Inc.) significantly raised product yields, especially when the reaction was performed on a larger scale (Notes 3 and 6).

3. The checkers found that reactions run on up to four times the present scale and rectified using a molecular still (wall temperature 110-120°C, 0.10 mm) gave yields of 89-94%. *Warning:* On this larger scale (i.e., four times the present scale) a brief run-away was experienced and some material which escaped from the condenser was caught in a trap; however, the yield was still excellent (94%).

4. On TLC [silica, visualization with 1.5% phosphomolybdic acid spray and heating] the product has an R_f of ca. 0.1 with ethyl acetate development and ca. 0.3 with methanol-dichloromethane [5:95] development. The ^1H NMR spectrum (CDCl_3) is as follows δ : 1.31 (t, 6 H, $J = 6.8$), 3.87 (d, 2 H, $J = 7$), 4.13 (m, 4 H), 5.34 (br s, 1 H, OH).

5. Five drops of reaction mixture is added to a mixture of 20 drops of diethyl ether and 1 drop of triethylamine. On TLC (Note 4) the product has an R_f of ca. 0.4 with ethyl acetate development. If TLC indicates the presence of diethyl hydroxymethylphosphonate an additional 5 g of dihydropyran and 10 drops of phosphorus oxychloride are added. The reaction is checked by TLC for completeness after 1 hr and is worked up at that time.

6. The checkers found that reactions run on up to nine times the present scale could be effected with only a small reduction in yield. Molecular still distillation (wall temperature 105-115°C, 0.10 mm) gave yields of 81-83%.

7. GLC analysis [0.5 x 200 cm 3% OV-17, 170°C, He flow = 30 mL/min] shows the product with a retention time of 5 min and a purity greater than 97%. The ^1H NMR spectrum (CDCl_3) is as follows δ : 1.35 (t, 6 H, $J = 7$), 1.4-1.9 (m, 6 H), 3.4-4.45 (m, 8 H), 4.7 (m, 1 H).

3. Discussion

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate is useful in the Wittig-Horner synthesis of enol ethers, which are intermediates in one-carbon homologations of carbonyl compounds.² This procedure is an adaptation of a general method for making dialkyl hydroxymethylphosphonates.³ An O-tetrahydropyranyl derivative also has been made from dibutyl hydroxymethylphosphonate, and diethyl hydroxymethylphosphonate has been O-silylated with tert-butylchlorodimethylsilane and imidazole.² Another useful congener in this series has been prepared by an Arbuzov reaction of methoxyethoxymethyl (MEM) chloride and triethyl phosphite.²

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2. Kluge, A. F.; Clousdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.
3. Zaripov, R. K.; Abramov, V. S. *Tr. Khim.-Met. Inst., Akad. Nauk Kaz. S.S.R.* **1969**, *5*, 50; *Chem. Abstr.* **1970**, *72*, 21745y.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate: Phosphonic acid, [[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-, diethyl ester (10); (71885-51-3)

Diethyl hydroxymethylphosphonate: Phosphonic acid, (hydroxymethyl)-, diethyl ester (8,9); (3084-40-0)

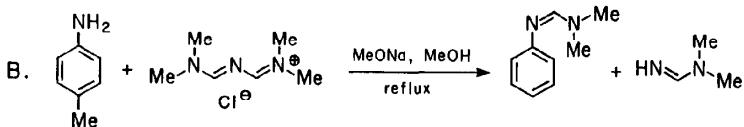
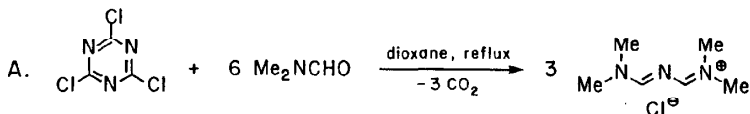
Diethyl phosphite: Phosphonic acid, diethyl ester (8,9); (762-04-9)

Paraformaldehyde: Poly(oxymethylene) (8,9); (9002-81-7)

Dihydropyran: 2H-Pyran, 3,4-dihydro- (8,9); (110-87-2)

Phosphorus oxychloride: Phosphoryl chloride (8,9); (10025-87-3)

(Methanimidamide, N,N-dimethyl-N'-(4-methylphenyl)-



Submitted by John T. Gupton and Steven A. Andrews.¹

Checked by T. V. RajanBabu and Bruce E. Smart.

1. Procedure

Caution! Cyanuric chloride is a lachrymator and causes burns on contact with the skin. All operations with this reagent should be carried out in a well-ventilated hood.

A. [3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride. A 1-L, one-necked, round-bottomed flask is equipped with a Claisen adapter, mechanical stirrer, reflux condenser, and mineral oil bubbler (Note 1). The flask is charged with cyanuric chloride (73.8 g, 0.4 mol) (Note 2), N,N-dimethylformamide (175.4 g, 2.4 mol) (Note 3) and 1,4-dioxane (100 mL) (Note 4). The resulting solution is stirred and heated (at approximately 85°C) for 2-3 hr while a considerable amount of carbon dioxide is evolved

(Note 5). When gas evolution is minimal, the reaction mixture is allowed to cool to room temperature; the product rapidly solidifies. The flask which contains the solid product is connected to an isopropyl alcohol/dry ice trap and the solvent is removed by evacuating the system to approximately 0.05 mm pressure. The crude product weighs 186-187 g (95%) and melts at 95-103°C (Notes 6, 7, 8).

B. *N,N*-Dimethyl-*N'*-*p*-tolylformamidine. A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar coated with Teflon is placed under a positive nitrogen pressure and charged with 100 mL of methanol (Note 9). Sodium metal (1.4 g, 0.06 mol) (Note 10) is then added in small portions. After all of the sodium has reacted, *p*-toluidine (6.4 g, 0.06 mol) (Note 11) is added and the resulting solution is stirred for 5 min. The iminium salt (10.6 g, 0.065 mol) produced in part A is added in one portion and the resulting mixture is refluxed with stirring overnight. The reaction mixture is cooled to room temperature and the solvent is removed on a rotary evaporator. The residue is taken up in chloroform (100 mL) and extracted twice with a saturated, aqueous solution of sodium bicarbonate (2 x 30 mL). The chloroform phase is dried over anhydrous magnesium sulfate, filtered, and the solvent is removed on a rotary evaporator. The residual dark brown liquid is distilled using a Kugelrohr apparatus (Note 12); the major fraction boils at 85-100°C (oven temperature), 0.4 mm, and yields 9.1-9.2 g (94-95%) of a pale yellow liquid (Notes 13 and 14).

2. Notes

1. The bubbler is connected to the condenser to monitor carbon dioxide evolution.

2. Cyanuric chloride was purchased from Aldrich Chemical Co. and was used without additional purification.

3. N,N-Dimethylformamide was purchased from Aldrich Chemical Co. and was dried over 3 Å molecular sieves prior to use.

4. The 1,4-dioxane was reagent grade and obtained from Fisher Scientific Corp. It was dried over 3 Å molecular sieves prior to use.

5. The reaction becomes very exothermic with substantial evolution of carbon dioxide within 30-45 min after heating is initiated. It may be necessary to cool the mixture with ice water if the evolution of gas becomes too vigorous.

6. The checkers obtained material free of N,N-dimethylformamide after drying for at least 18 hr. The checkers found variable melting points that depended on the rate of heating. The submitters obtained 195 g (99%) of product which melted at 81-83°C after drying overnight at 1-6 mm of pressure, and indicated that the product may contain a small amount of N,N-dimethylformamide, but is suitable for use without additional purification. [3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride is reported to melt at 101-103°C.²

7. The product is very hygroscopic and should be handled under a moisture-free environment. If the iminium salt is kept dry it has a substantial shelf life. The submitters recommend storing the product in a desiccator over anhydrous calcium sulfate.

8. The product has the following spectral characteristics: IR (CHCl_3) cm^{-1} : 1610 (C=N); ^1H NMR (CDCl_3) δ : 3.27 (s, 6 H, two CH_3), 3.43 (s, 6 H, two CH_3), 9.57 (s, 2 H, $-\text{CH}=\text{N}$).

9. The methanol which was used was reagent grade and was dried over 3 Å molecular sieves.

10. Sodium metal was obtained from Fisher Scientific Corp.

11. p-Toluidine was reagent grade and was obtained from the Eastman Chemical Co.

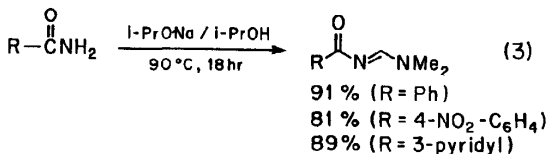
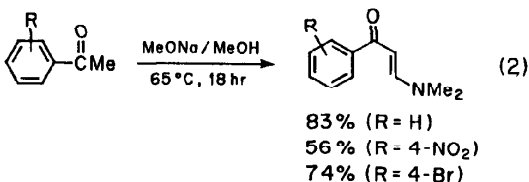
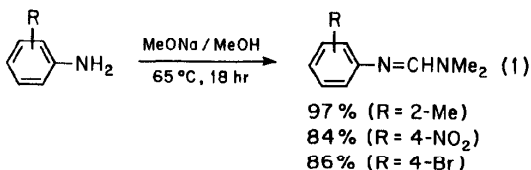
12. The Kugelrohr apparatus was obtained from the Aldrich Chemical Co.

13. The submitters obtained 8.3-9.1 g (86-94%) boiling at 85-107°C, 0.4 mm. The reported bp of N,N-dimethyl-N'-p-tolylformamidine is 163°C (30 mm).³ A gas chromatographic analysis of the product using a 1/4" x 10' column packed with 5% carbowax 20 M supported on 80-100 mesh chromosorb N exhibited a single peak with a retention time of 4.8 min at an oven temperature of 220°C with a flow rate of 60 cc/min. The checkers redistilled the product to obtain colorless material, bp 69.5°C (0.2 mm), which was analyzed. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2$: C, 74.03; H, 8.70; N, 17.27. Found C, 73.57; H, 8.51; N, 17.50.

14. The product has the following spectral characteristics: IR (neat) cm^{-1} : 3030 (aromatic CH), 1635 (C=N), 1600 (C=C), ^1H NMR (CDCl_3) δ : 2.23 (s, 3 H, aromatic CH_3), 2.87 (s, 6 H, $-\text{N}(\text{CH}_3)_2$), 6.83 (d, 2 H, J = 8, aromatic CH), 7.06 (d, 2 H, J = 8, aromatic CH), 7.43 (s, 1 H, $-\text{CH}=\text{N}-$).

3. Discussion

[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride ("Gold's reagent"),⁴ the preparation of which is described in part A of the procedure, is a general β -dimethylaminomethylenating agent which reacts successfully with amines (eq. 1) to produce amidines,⁵ with ketones (eq. 2) to produce enamines,⁶ and with amides (eq. 3) to produce acylamidines.⁷



All reactions proceed in high yield and under mild conditions produce relatively pure products. The most effective β -dimethylamino methylenating agents currently available are the formamide acetals,⁸ some of which are available commercially.⁹ They are, however, expensive, moisture and heat

sensitive, and require potent, mutagenic alkylating agents for their preparation. Under some circumstances they also necessitate high reaction temperatures and long reaction times. Alternatively, "Gold's reagent" is prepared in a single step, and in nearly quantitative yield, without purification, from inexpensive raw materials. The reaction of "Gold's reagent" with an amine or other substrate can be carried out at relatively low temperatures (65-90°C) and moderate reaction times (12-24 hr).

The significance of the amino methylenated amines, ketones, and amides as important compounds and reaction intermediates is well-documented^{5,6,7} and the use of "Gold's reagent," therefore, provides an efficient, economical, and clean method for obtaining such substances.

1. Department of Chemistry, University of Central Florida, P.O. Box 25000, Orlando, FL 32816.
2. Gold, H. *Angew. Chem.* **1960**, *72*, 956; *Chem. Abstr.* **1962**, *57*, 4542d.
3. Meerwein, H.; Florian, W.; Schon, N.; Stopp, F. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1.
4. We have named this compound "Gold's Reagent" to simplify its common usage nomenclature.
5. Patai, S. "The Chemistry of Amidines and Imidates", Wiley: New York, 1975; Chapter 7.
6. For a recent review of the synthetic importance of enamines see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.
7. (a) Lin, Y.; Lang, S. A.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160; (b) Lin, Y.; Lang, S. A.; Petty, S. R. *J. Org. Chem.* **1980**, *45*, 3750.

8. Abdulla, R.; Brinkmeyer, R. *Tetrahedron Lett.* **1979**, 1675; Simchen, G. In "Advances in Organic Chemistry: Methods and Results", Böhme, H. and Viehe, H., Eds.; Wiley: New York, 1979; Vol. 9, Pt. 2, pp. 393-526.
9. Aldrich Chemical Co., Milwaukee, Wisconsin.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

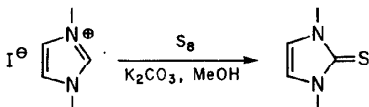
Cyanuric chloride: s-Triazine, 2,4,6-trichloro- (8); 1,3,5-Triazine, 2,4,6-trichloro- (9); (108-77-0)

[3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride: Ammonium, [[[dimethylamino)methylene]amino]methylene]dimethyl-, chloride (8); Methanaminium, N-[[[(dimethylamino)methylene]amino]methylene]-N-methyl-, chloride (9); (20353-93-9)

p-Toluidine (8); Benzenamine, 4-methyl- (9); (106-49-0)

N,N-Dimethyl-N'-p-tolylformamidine: Formamidine, N,N-dimethyl-N'-p-tolyl- (8); Methanimidamide, N,N-dimethyl-N'-(4-methylphenyl)- (9); (7549-96-4)

1,3-DIMETHYLIMIDAZOLE-2-THIONE
(2H-Imidazole-2-thione, 1,3-dihydro-1,3-dimethyl-)



Submitted by Brian L. Benac,^{1a} Edward M. Burgess,² and
Anthony J. Arduengo, III.^{1b}

Checked by David K. Brittelli, Joseph Burlak, Jr., and Bruce E. Smart.

1. Procedure

In a dry, 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a drying tube are placed 44.8 g (0.20 mol) of 1,3-dimethylimidazolium iodide (Note 1), 35.0 g (0.25 mol) of anhydrous potassium carbonate, 6.5 g (0.20 mol) of sulfur (Note 2) and 300 mL of methanol (Note 3). The mixture is stirred for 40 hr at room temperature. The cloudy yellow mixture is filtered through a pad of Celite (Note 4) and the filter cake is washed with 80 mL of dichloromethane. The combined mother liquor and wash is evaporated to dryness on a rotary evaporator. The orange residue is dissolved in 500 mL of hot water and the hot solution is filtered to remove insoluble impurities. The aqueous filtrate is reheated and the product crystallizes on cooling. The white needles are collected by filtration, washed with 50 mL of cold water and air dried for 1 hr. The mother liquor is concentrated to yield a second crop of crystals to give a total of 15-16 g (58-62%) of pure 1,3-dimethylimidazole-2-thione, mp 182-183.5°C (Note 5).

2. Notes

1. The imidazolium iodide salt is conveniently prepared by the following procedure: A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, thermometer, water-cooled condenser, and a magnetic stirrer is charged with 200 mL of anhydrous methylene chloride and 82.1 g (1.0 mol) of 1-methylimidazole (from the Aldrich Chemical Company, Inc.). The solution is cooled and maintained at 5°C while 143.0 g (1.01 mol) of iodomethane in 75 mL of anhydrous methylene chloride is added dropwise over a period of 30 min. When the addition is completed, the cooling bath is removed and the reaction mixture is stirred for 30 min at room temperature. Methylene chloride is removed on a rotary evaporator to yield 213.6-216.7 g (95-97%) of 1,3-dimethylimidazolium iodide, mp 81-83°C, ^1H NMR (d_6 -DMSO) δ : 3.89 (s, 6 H), 7.73 (s, 2 H), 9.16 (s, 1 H). The submitters report the following spectral data: ^1H NMR (d_6 -DMSO) δ : 4.08 (s, 6 H), 7.75 (s, 2 H), 9.86 (s, 1 H); ^{13}C NMR (d_6 -DMSO) δ : 36.10 (s), 123.04 (s), 136.69 (s).

The submitters report that the bromide and methyl sulfate salts of the 1,3-dimethylimidazolium cation gave similar yields in the thione synthesis.

2. Lac (precipitated) sulfur gives the best results. The checkers found that with sublimed sulfur (Fisher Scientific Company, Laboratory Grade) the yield of thione product is 12.5-12.8 g (49-50%).

Lac sulfur is prepared by boiling a suspension of 33 g of calcium oxide and 50 g of sublimed sulfur (Fisher Scientific Company) in 200 mL of water for 30 min, then filtering the hot solution and acidifying the clear filtrate to pH 5 with hydrochloric acid. The precipitated sulfur is collected, washed with water, and dried in a vacuum desiccator.

3. A.C.S. grade methanol from the Fisher Scientific Company was used without further purification. The submitters report that attempts to use ethanol or water as solvents were unsuccessful.

4. The reaction mixture has a distinct odor of sulfur and should be handled in a hood. The product is odorless.

5. The submitters report a mp of 182-184°C for material which was recrystallized from water or sublimed under reduced pressure. The product shows the following ^1H NMR spectrum (CDCl_3) δ : 3.58 (s, 6 H), 6.71 (s, 2 H). The submitters report the following spectral data: ^1H NMR (CDCl_3) δ : 3.6 (s, 6 H), 6.68 (s, 2 H); ^{13}C NMR (d_6 -DMSO) δ : 34.34 (s), 117.82 (s), 161.87 (>); IR (CHCl_3) cm^{-1} : 2940 (C-H), 1450, and 1380.

3. Discussion

1,3-Dimethylimidazole-2-thione was first reported by Ansell, Forkey and Moore³ who studied the X-ray crystal structure of this thione. No detailed synthesis of the thione has appeared in the chemical literature. This unusual thione has been used as a precursor to unusual thione ylides,^{4,5} tricoordinate sulfuranes⁶ and as a desulfurizing agent for a thirane.⁵ The thione also has remarkable anti-oxidant properties.⁷ Compared to tetramethylthiourea, 1,3-dimethylimidazole-2-thione is remarkably resistant to desulfurization.

This procedure has been used to synthesize a variety of 1,3-dialkylimidazole 2-thiones. Other imidazole-2-chalcogenones (Se, Te) can be synthesized by similar procedures.

1. (a) Department of Chemistry, The Roger Adams Laboratory, University of Illinois-Urbana, IL 61801. (b) Present address: E. I. du Pont de Nemours & Co., Central Research and Development Department, E328/201, Wilmington, DE 19898.
2. Department of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332.
3. Ansell, G. B.; Forkey, D. M.; Moore, D. W. *J. Chem. Soc., Chem. Commun.* **1970**, 56.
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7. Arduengo, A. J.; Burgess, E. M., unpublished results.

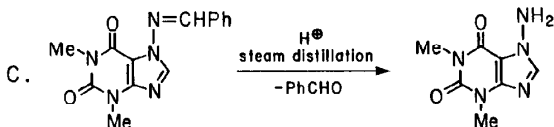
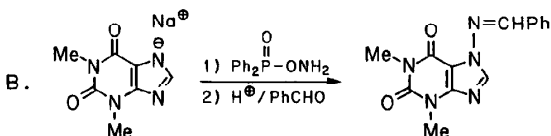
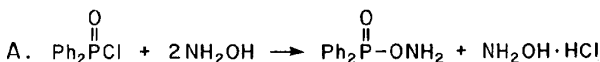
Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

1,3-Dimethylimidazole-2-thione: 4-Imidazoline-2-thione, 1,3-dimethyl- (8);
 2H-Imidazole-2-thione, 1,3-dihydro-1,3-dimethyl (9); (6596-81-2)
 1-Methylimidazole: Imidazole, 1-methyl- (8); 1H-Imidazole, 1-methyl- (9);
 (616-47-7)
 Iodomethane: Methane, iodo- (8,9); (74-88-4)
 Sulfur (S₈) (8); Octathiocane (9); (10544-50-0)

**ELECTROPHILIC N-AMINATION OF IMIDE SODIUM SALTS WITH
O-DIPHENYLPHOSPHINYLDIHYDROXYLAMINE (DPH): 7-AMINOTHEOPHYLLINE
(1H-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl-)**



Submitted by W. Klötzer, J. Stadlwieser, and J. Raneburger.¹

Checked by Michael J. Luzzio and Andrew S. Kende.

1. Procedure

A. *O*-Diphenylphosphinyldihydroxyamine.² A 500-mL, round-bottomed flask, equipped with a reflux condenser, drying tube, an efficient mechanical stirrer, a dropping funnel and a nitrogen-inlet tube, is charged with 300 mL of anhydrous methylene chloride, 16.5 g (0.5 mol) of hydroxylamine base (Note 1), and 1.0 g of dry sodium bicarbonate. While the suspension is stirred vigorously at -30°C (bath temperature), a solution of 52.06 g (0.22 mol) of diphenylphosphinyl chloride (Note 2) in 70 mL of anhydrous methylene chloride

is added under a nitrogen atmosphere at a constant rate within 30 min. The resulting thick suspension is stirred at -30°C for 2 hr and for an additional 2 hr after the cooling bath is removed. The reaction mixture is filtered through a sintered-glass funnel (porosity 3) and the residue is washed with two 80-mL portions of methylene chloride. The methylene chloride is removed from the colorless solid by a stream of air for 2 hr. The dry solid, still on the funnel, is then mixed thoroughly with 200 mL of deionized water. The water is removed by suction. The same operation is performed sequentially with 150 mL of 5% aqueous sodium bicarbonate solution and then with two 150-mL portions of water. This solid, which retains water tenaciously, is dried by suction and by pressing down on the funnel for several hours, followed by drying in a phosphorus pentoxide-charged vacuum desiccator until its weight is constant (24 hr) to give 36 g (70%) of impure O-diphenylphosphinylhydroxylamine, mp $120^{\circ}\text{--}135^{\circ}\text{C}$, with decomposition.

A 500-mL, two-necked flask, equipped with a reflux condenser and a drying tube, is charged with 240 mL of anhydrous ethanol. The solvent is preheated to 70°C and a 12-g portion of this finely powdered dry product is added all at once. The resulting suspension is refluxed for 2-3 min when almost all of the solid has dissolved. The hot solution is filtered as quickly as possible through a sintered-glass funnel (porosity 3) and the filtrate is chilled to 0°C for 30 min. Isolation of the crystalline deposit and washing with 20 mL of ether provides 7.8 g of pure product. Recrystallization of three 12-g portions furnishes 23.4 g (44%) of O-diphenylphosphinylhydroxylamine, mp $>140^{\circ}\text{C}$, with decomposition (Note 3).

B. 7-Benzylideneaminotheophylline. A 2000-mL, round-bottomed flask, equipped with an efficient mechanical stirrer, thermometer, and drying tube, is charged with 600 mL of anhydrous N-methylpyrrolidone (Note 4) and 20.2 g

(0.1 mol) of anhydrous theophylline sodium salt (Note 5). The flask is cooled with an ice-salt bath to 0°C (internal temperature). Then 23.4 g (0.1 mol) of *O*-diphenylphosphinylhydroxylamine is added in three equal portions while the suspension is stirred vigorously. After the ice-salt bath is removed, the resulting viscous suspension is stirred for 6 hr at 20°C.

After the solution is diluted with 1200 mL of water, the pH is adjusted to 1-2 with concd hydrochloric acid and the mixture stirred at 5°C for 1 hr. The precipitated diphenylphosphinic acid is isolated by filtration and washed with 50 mL of water (Note 6). The filtrate is placed in a 2000-mL, round-bottomed flask, equipped with a reflux condenser and an efficient mechanical stirrer. A solution of 20 mL of benzaldehyde in 50 mL of ether is added and the mixture is stirred vigorously for 20 min. The precipitate that forms is isolated by filtration and washed sequentially with 50 mL of water and 50 mL of ether to yield 19.6 g (69%) of 7-benzylideneaminotheophylline, mp 207-209°C.³ An analytical sample may be prepared by recrystallization from ethanol (mp 209°C).

C. 7-Aminotheophylline. The reaction flask of a steam distillation apparatus is charged with 19.6 g (0.069 mol) of 7-benzylideneaminotheophylline and 100 mL (0.1 mol) of 1 N hydrochloric acid. The suspension is steam distilled until no more benzaldehyde is detected in the distillate (Note 7). The resulting clear solution in the reaction flask is concentrated by rotary evaporation to a volume of 30 mL, adjusted to pH 10 with concentrated ammonium hydroxide, transferred to a separatory funnel and extracted with five 60-mL portions of chloroform. The combined chloroform extracts are dried with anhydrous sodium sulfate, filtered and concentrated to dryness by rotary evaporation. The residue is recrystallized from 75 mL of water to afford 11.3 g (84%) of 7-aminotheophylline, mp 222°C.³

2. Notes

1. Hydroxylamine base has been prepared by the method of Lecher and Hofmann.⁴ The free base can be stored in a tightly stoppered flask at -20°C for several days. The checkers found it expedient to prepare free hydroxylamine by a modification of the Lecher and Hofmann procedure in which a Schlenk tube under dry N_2 was used to filter the NaCl precipitate and the NH_2OH base was crystallized from the filtrate at -30°C , then isolated by inverting the Schlenk apparatus and filtering the product (74% yield from the hydrochloride).

2. Diphenylphosphinyl chloride can be purchased from Aldrich Chemical Company, Inc. or from EGA-Chemie, D-7924 Steinheim, West Germany (an Aldrich Chemical Company). Diphenylphosphinyl chloride can also be prepared by oxygen-mediated oxidation of diphenylchlorophosphine⁵ (purchased from Fluka AG, CH-9470 Buchs, Switzerland).

3. The recrystallization should be performed as quickly as possible in portions below 15 g. Prolonged heating in ethanolic solution causes substantial losses. The pure, dry compound can be stored in a tightly stoppered flask at 0°C for at least 6 months without loss of aminating capacity. The submitters report that the pure compound showed no signs of spontaneous decomposition during 4 years of use, except when heated to $>140^{\circ}\text{C}$, where the compound decomposes with effervescence.

4. N-Methylpyrrolidone (purum grade) was purchased from Fluka AG, CH-9470 Buchs, Switzerland, dried over calcium hydride, and vacuum distilled [bp $78-79^{\circ}\text{C}$ (12 mm)].

5. The sodium salt of theophylline was obtained as follows: to a solution of 36.34 g (0.2 mol) of theophylline in 120 mL of 50% aqueous ethanol at 80°C was added 50 mL (0.2 mol) of aqueous 4 N sodium hydroxide. Chilling to 0°C, filtration of the precipitate, washing with 50 mL of 96% ethanol, then with 100 mL ether, and drying in a vacuum desiccator over phosphorus pentoxide provides 28.0 g of the anhydrous salt.

6. The recovered and dried diphenylphosphinic acid, 19.6 g (90%), is ready to be recycled to diphenylphosphinyl chloride.^{6,7}

7. Traces of benzaldehyde can be detected with Brady's reagent (2,4-dinitrophenylhydrazine sulfate solution) or by its characteristic smell.

3. Discussion

Electrophillic N-aminations of imide salts have been performed with hydroxylamine-O-sulfonic acid (HOSA),^{8,9,10} O-(2,4-dinitrophenyl)-hydroxylamine,^{11,12} and O-mesitylenesulfonylhydroxylamine (MSH).¹¹ The use of HOSA is mainly restricted to aqueous reaction media.^{8,9} O-(2,4-Dinitrophenyl)hydroxylamine, MSH, and O-diphenylphosphinylhydroxylamine (DPH) can be applied in anhydrous or even non-polar solvents. O-(2,4-Dinitrophenyl)hydroxylamine and MSH require N-protected hydroxylamine for their preparation.^{11,12} MSH has been found to be explosive.^{13,14} DPH has the advantage of being prepared directly from unprotected hydroxylamine and seems to have no tendency toward spontaneous decomposition. The possibility of recycling diphenylphosphinic acid may be regarded as a further advantage. The advantage of using unprotected hydroxylamine to prepare DPH is partially negated by the required somewhat delicate preparation and handling of the free hydroxylamine base. The large amount of solvent that is sometimes required

because of the low solubility of DPH and the resulting diphenylphosphinic acid salt may be regarded as a disadvantage too.

O-Diphenylphosphinylhydroxylamine has also been used to aminate carbanions,^{15,16} tertiary phosphines, and thio ethers.²

TABLE
N-AMINO COMPOUNDS FROM IMIDE SODIUM SALTS AND DPH^a

Educt		Solvent ^b	Product	Yield	Lit.
Alkali Salt					
Imidazole		DMF	1-Aminoimidazole	28%	3
2-Nitroimidazole		NMP	1-Amino-2-nitro- imidazole	40%	3
2-Methyl-4(5)- nitroimidazole		NMP	1-Amino-2-methyl- 4-nitroimidazole	30%	3
Theobromine		DMF	1-Aminothobromine	71%	3
Theophylline		NMP	7-Aminothephylline	60%	3
Phthalimide		DMF	N-Aminophthalimide	90%	3

^aDPH = O-diphenylphosphinylhydroxylamine.

^bDMF = anhydrous dimethylformamide.

NMP = anhydrous N-methylpyrrolidone.

1. Institut für Organische und Pharmazeutische Chemie, Universität Innsbruck, A-6020 Innsbruck, Innrain 52a, Austria.
2. The method represents a modification of a recently published preparation: Harger, M. J. P. *J. Chem. Soc., Perkin Trans 1* **1981**, 3284.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

O-Diphenylphosphinylhydroxylamine: Hydroxylamine, O-(diphenylphosphinyl)- (10); (72804-96-7)

7-Aminotheophylline: 1H-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl- (11); (81281-58-5)

Hydroxylamine hydrochloride (8,9); (5470-11-1)

Diphenylphosphinyl chloride: Phosphinic chloride, diphenyl- (8,9); (1499-21-4)

7-Benzylideneaminotheophylline: 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-7-[(phenylmethylene)amino]- (11); (81281-59-6)

N-Methylpyrrolidone: 2-Pyrrolidinone, 1-methyl- (8,9); (872-50-4)

Theophylline (8); 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl- (9); (58-55-9)

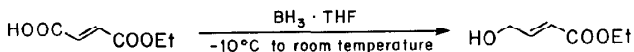
Diphenylphosphinic acid: Phosphinic acid, diphenyl- (8,9); (1707-03-5)

Benzaldehyde (8,9); (100-52-7)

Diphenylchlorophosphine: Phosphinous chloride, diphenyl- (8,9); (1079-66-9)

ETHYL 4-HYDROXYCROTONATE

(2-Butenoic acid, 4-hydroxy-, ethyl ester, (E)-)



Submitted by Andrew S. Kende and Pawel Fludzinski.¹

Checked by Cynthia McClure and Edwin Vedejs.

1. Procedure

A dry, 2-L, one-necked, round-bottomed flask is equipped with a 1-L pressure-equalizing funnel and a large magnetic stirring bar. The system is flame-dried under an internal atmosphere of dry nitrogen (Note 1). The flask is charged with 300 mL of anhydrous tetrahydrofuran (Note 2) and 100 g of monoethyl fumarate. The solution is then stirred under nitrogen and brought to about -5°C using an ice-salt/methanol bath (-10°C) (Note 3). A 1 M solution of 100 mL (0.10 mol) of borane-tetrahydrofuran complex (Note 4) is *cautiously* added dropwise (rapid H₂ evolution occurs) with rigorous temperature control to avoid an exothermic reaction. The ice-salt bath is maintained in position throughout the 90 min of addition. The stirred reaction mixture is then gradually allowed to warm to room temperature over the next 8-10 hr. The reaction is carefully quenched at room temperature by dropwise addition of 1:1 water-acetic acid (ca. 20 mL) with stirring until no more gas evolution occurs. The reaction is concentrated at room temperature

and water pump pressure to a slurry by removal of most of the tetrahydrofuran. The slurry is carefully poured over a 20-min period into 300 mL of ice cold, saturated sodium bicarbonate solution with mechanical stirring to avoid precipitation of solids, and the product is extracted with 300 mL of ethyl acetate. The aqueous layer is again extracted with 100 mL of ethyl acetate. The organic layers are combined, washed once with 200 mL of saturated sodium bicarbonate, then dried well with anhydrous magnesium sulfate.

Solvent removal at reduced pressure gives 61 g (67% yield) of essentially pure ethyl hydroxycrotonate (Note 5).

An analytical sample may be prepared by quick distillation (or Kugelrohr distillation) at 117-120°C (15 mm), but there is significant loss of material because of decomposition in the distillation pot. From 1 g of product, 0.72 g of pure material is obtained in this way, and recovery decreases as scale of distillation increases.

2. Notes

1. This is accomplished by passing a stream of dry nitrogen through the reaction vessel. During the reaction, a slight positive pressure of nitrogen is maintained throughout the apparatus.

2. The tetrahydrofuran is freshly distilled from sodium and benzophenone.²

3. The flask is cooled with the ice-salt/methanol bath for 30 min before the next addition to insure complete cooling of the solution.

4. Borane-tetrahydrofuran is commercially available from Aldrich Chemical Company, Inc. When a fresh bottle is used, titration is not necessary.

5. NMR data for ethyl 4-hydroxycrotonate are as follows (100 MHz, CDCl_3): δ 1.30 (t, 3 H, $J = 7$), 3.58 (br s, 1 H), 4.17 (q, 2 H, $J = 7$), 4.30 (m, 2 H), 6.03 (dt, 1 H, $J = 16$), 6.98 (dt, 1 H, $J = 16$).

3. Discussion

Ethyl (or methyl) 4-hydroxycrotonate has previously been prepared in 51% yield by silver oxide-assisted solvolysis of methyl 4-bromocrotonate,³ or in 94% yield by reaction of glycolaldehyde with (carbomethoxymethylene)triphenylphosphorane.⁴ Both procedures require very expensive starting materials or reagents. Several multistep procedures for preparing the title compound have also been reported.⁵ The procedure described above represents a convenient one-step alternative for preparing ethyl 4-hydroxycrotonate, requiring inexpensive starting materials and reagents. This procedure relies on the selective reduction of a carboxylic acid in the presence of a carboxylic ester with borane, which is well documented.⁶

Ethyl 4-hydroxycrotonate has proven to be a valuable intermediate in synthetic chemistry. It has been used in alkaloid synthesis³ or as a dipolarophile in dipolar cycloadditions.⁷ Furthermore, ethyl 4-hydroxycrotonate can be readily oxidized to ethyl 4-oxocrotonate,⁴ which has also served as a valuable precursor in synthesis.⁸

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

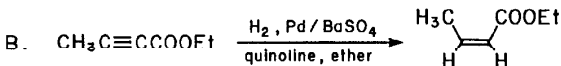
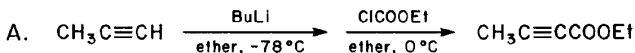
Ethyl 4-hydroxycrotonate: Crotonic acid, 4-hydroxy-, ethyl ester, (E)- (8);

2-Butenoic acid, 4-hydroxy-, ethyl ester. (E)- (9); (10080-68-9)

Monoethyl fumarate: Fumaric acid, monoethyl ester (8); 2-Butenedioic acid (E)-, monoethyl ester (9); (2459-05-4)

Borane-tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1:1) (8,9); (14044-65-6)

ETHYL ISOCROTONATE
(Ethyl (Z)-crotonate)



Submitted by Michael J. Taschner, Terry Rosen, and Clayton H. Heathcock.¹

Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. Ethyl tetrolate. A 3-L, three-necked, round-bottomed flask is equipped with an overhead mechanical stirrer and charged with 1000 mL of anhydrous ether (Note 1). One neck is fitted with a gas-inlet joint connected to a nitrogen line equipped with a mineral oil bubbler. The second neck is fitted with a low-temperature thermometer, and the third is closed with a rubber serum cap after nitrogen has been passed through the flask for a few minutes. The flask is then immersed in a dry ice-acetone bath. While the ether is cooling, 85 mL (60.0 g, 1.50 mol) of propyne (Note 2) is condensed into a flask (Note 3). The stopper is removed briefly, the cold (-78°C) propyne is poured into the flask through a powder funnel inserted into the neck, and stirring is commenced. The stopper is replaced, and 667 mL of a 1.5 M solution of butyllithium in hexane is introduced by syringe at such a rate that the internal temperature does not exceed -65°C (Notes 4, 5, 6). During

the butyllithium addition a copious white precipitate appears. The slurry is stirred at -78°C for 30 min, and 134 mL (152 g, 1.4 mol) of ethyl chloroformate (Note 7) is added. At this point, the acetone-dry ice bath is replaced by an ice bath and the reaction mixture is stirred overnight. During this time the ice bath will melt and the reaction mixture should eventually reach room temperature. The mixture is poured onto 400 g of crushed ice, the layers are separated, and the aqueous phase is extracted with two 200-mL portions of ether. The ether solutions are combined, washed with brine and dried over anhydrous MgSO_4 . After filtration, the ether is removed with a rotary evaporator (Note 8). The residue is distilled at aspirator pressure to obtain 107-108 g (95-97%) of ethyl tetrolate, bp $60-64^{\circ}\text{C}$ (20 mm) [lit.² 105°C (90 mm)] (Note 9).

B. *Ethyl isocrotonate*. An oven-dried, 500-mL hydrogenation flask equipped with a side arm fitted with a rubber serum cap and a magnetic stirring bar, is charged with 0.4 g of 5% palladium on barium sulfate (Note 10), 0.4 g of quinoline and 200 mL of anhydrous ether. The flask is attached to an atmospheric pressure hydrogenation apparatus (Note 11) and flushed with hydrogen. Ethyl tetrolate (23.2 mL, 22.4 g, 0.2 mol) is introduced into the hydrogenation flask with a syringe, and stirring is commenced. The progress of the reaction may be monitored by the uptake of hydrogen (theoretical = 4500 mL), by gas chromatography, or by removing aliquots which are concentrated and analyzed by ^1H NMR, monitoring the disappearance of the methyl singlet at δ 1.95; a total hydrogenation time of 10-15 hr is required (Note 12). After hydrogenation is complete, the catalyst is removed by filtration of the reaction mixture through a Celite pad. The ether is removed with a rotary evaporator (Note 8) to obtain 21.1-22.4 g (93-98%) of ethyl isocrotonate as a light yellow liquid. This material contains traces of quinoline, but is of

suitable purity for many uses (Note 6, 13). The quinoline may be removed, if desired, by washing the ether solution with 1 M aqueous acetic acid, followed by aqueous sodium carbonate, or by distillation at atmospheric pressure, bp 128-132°C [lit.³ bp 129-130.5°C] (Note 14).

2. Notes

1. Although stirring can be done with a large magnetic stirring bar, the reaction mixture becomes rather thick as the 1-lithiopropyne is formed, and effective stirring is difficult. The checkers found that the yield in this step is only 11% when a magnetic stirrer is used.

2. Methylacetylene (technical grade) from Linde Division of the Union Carbide Corporation was employed. The checkers used Matheson Lecture bottles.

3. The propyne is passed directly from the tank or lecture bottle to a cold-finger condenser filled with a slush of isopropyl alcohol and dry ice. The condenser is attached to a 200-mL, three-necked flask equipped with a gas-inlet adapter and a glass stopper. The flask has been previously calibrated to hold 85 mL of liquid.

4. Alternatively, the butyllithium solution may be forced into the reaction flask by means of an 18 gauge cannula inserted through the serum cap.

5. Butyllithium was obtained from Foote Mineral Co., Johnsonville, Tennessee. It may be standardized by a double titration procedure.⁴

6. If care is not taken in the formation of 1-lithiopropyne, the final product can be contaminated with as much as 10% of an impurity, which is presumed to be ethyl pentanoate. This impurity has a GLC retention time on conventional packed columns that is quite similar to that of ethyl (E)-crotonate. The by-product presumably results from the presence of butyl-

lithium when the ethyl chloroformate is added. The submitters have not observed the formation of this product if care is taken to maintain the reaction temperature below -65°C during addition of the butyllithium to the propyne.

7. Ethyl chloroformate (practical grade) was obtained from Matheson Coleman & Bell Manufacturing Chemists, Inc., Cincinnati, Ohio 45212, and used without purification.

8. It is important that the rotary evaporator bath be kept at $5\text{--}10^{\circ}\text{C}$, or some of the product will be lost by evaporation.

9. The infrared spectrum (neat) has absorptions at 2250, 1700, and 1260 cm^{-1} . The ^1H NMR spectrum (CDCl_3) is as follows δ : 1.23 (t, 3 H, $J = 7$), 1.95 (s, 3 H), 4.07 (q, 2 H, $J = 7$).

10. The catalyst was obtained from The American Platinum Works, Newark, N.J.

11. The submitters employed an apparatus similar to that described by Wiberg.⁵

12. The hydrogenation can also be carried out without special apparatus by the following method. The ether solution is placed in a 500-mL, three-necked flask fitted with a fritted gas inlet tube, a rubber serum cap, an oil bubbler, and a magnetic stirring bar. The catalyst, quinoline and ethyl tetrolate are introduced, and the reaction flask is cooled in an ice bath. Hydrogen is bubbled through the cold solution at such a rate as to maintain atmospheric pressure in the flask as evidenced by the oil bubbler. When using this technique, it is necessary to monitor the course of hydrogenation by GLC or ^1H NMR. However, the rate of hydrogenation decreases rather abruptly after one molar equivalent has been absorbed, and there is little danger of over-hydrogenation.

13. Capillary GLC analysis (12 m, cross-linked methyl silicone, programmed, 45°C, 3°C/min, retention time of ethyl (Z)-crotonate, 2.5 min). Ethyl (E)-crotonate has a retention time of 2.95 min under the same conditions. Careful quantitative analysis reveals that the ratio of Z and E isomers is reproducibly in the range 58:1 to 59:1.

14. The infrared spectrum (neat) has absorptions at 3040, 1710, 1640, 1175, 1025, and 810 cm^{-1} . The ^1H NMR spectrum is as follows (CDCl_3) δ : 1.23 (t, 3 H, J = 7), 2.05 (dd, 3 H, J = 2, 7), 4.03 (q, 2 H, J = 7), 5.62 (dq, 1 H, J = 12, 2), 6.19 (dq, 1 H, J = 12, 7).

3. Discussion

A previous *Organic Syntheses* procedure for the preparation of isocrotonic acid involves the stereospecific Favorskii rearrangement of 1,3-dibromo-2-butanone.⁶ However, the procedure is rather laborious and, in our hands, gives only a modest overall yield of acid. Isocrotonic acid has also been prepared by carbonation of cis-propenyllithium⁷ and by sodium amalgam reduction of β -chloroisocrotonic acid.⁸ The present procedure for semihydrogenation of ethyl tetrolate is based on early work of Bourguet⁹ and of Allan, Jones and Whiting.¹⁰ The procedure for acylation of propyne is general and may be employed for the preparation of other α,β -acetylenic esters.¹¹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Ethyl isocrotonate: Crotonic acid, ethyl ester, (Z)- (8); 2-Butenoic acid, ethyl ester, (Z)- (9); (6776-19-8)

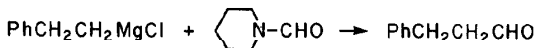
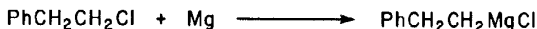
Ethyl tetrolate: Tetrollic acid, ethyl ester (8); 2-Butynoic acid, ethyl ester (9); (4341-76-8)

Propyne (8); 1-Propyne (9); (74-99-7)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Ethyl chloroformate: Formic acid, chloro-, ethyl ester (8); Carbonochloridic acid, ethyl ester (9); (541-41-3)

(Benzenepropanal)

Submitted by George A. Olah and Massoud Arvanaghi.¹

Checked by David Heiler and Martin F. Semmelhack.

1. Procedure

Magnesium (2.88 g, 0.12 mol), 300 mL of anhydrous tetrahydrofuran (Note 1), and 10 mg of iodine are placed in a 1-L, three-necked, round-bottomed flask fitted with a stirrer, dropping funnel with a pressure-equalizing tube and a reflux condenser connected to nitrogen flow line. Nitrogen is passed through the solvent for 15 min and a constant flow of nitrogen is maintained throughout the reaction. A solution of 14.06 g (0.1 mol) of (2-chloroethyl)benzene (Note 2) in 50 mL of tetrahydrofuran is placed in the dropping funnel. About 2 mL of this solution is added to the reaction mixture and the reaction is initiated by gently heating the flask (with a heat gun). Once the reaction has started, as evidenced by the disappearance of iodine color, the rest of the (2-chloroethyl)benzene solution is added dropwise at such a rate that a gentle reflux is maintained throughout the addition. The resulting solution is stirred for an additional 1 hr at 23°C, followed by

heating at reflux for 8 hr. The reaction vessel is cooled to 0°C and a solution of 13.56 g (0.12 mol) of N-formylpiperidine (Note 3) in 50 mL of dry tetrahydrofuran is added dropwise (Note 4). The mixture is brought to 23°C and stirred for another 15 min.

The reaction mixture is quenched by the addition of 25 mL of ice water, and slowly acidified to pH 2 with 75 mL of 3 N hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with three 75-mL portions of ether. The extracts are combined with the original ether layer, washed successively with 50 mL of water, two 50-mL portions of aqueous 10% sodium bicarbonate, and 50 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the magnesium sulfate is removed by filtration, the solvent is removed at aspirator vacuum on a rotary evaporator and the residue is distilled through a short column to give 8.8-10.2 g (66-76%) of 3-phenylpropionaldehyde, bp 87°C (1.0 mm) (Notes 5, 6, and 7).

2. Notes

1. Technical grade tetrahydrofuran was predried for a few days over sodium hydroxide. It was then heated under reflux over sodium wire with benzophenone until it developed a permanent blue color and distilled with exclusion of atmospheric moisture. (*Caution:* See p. 976 of *Org. Synth. Coll. Vol. V* for a warning regarding purification of tetrahydrofuran.)

2. The (2-chloroethyl)benzene was purchased from Eastman Organic Chemicals and used without further purification.

3. N-Formylpiperidine was obtained from Reilly Tar and Chemicals or from Aldrich Chemical Company and used without further purification.

4. Too rapid addition of N-formylpiperidine should be avoided as it can result in a cake-like solid which hinders mixing of the reaction mixture. Efficient stirring is crucial to optimum yields.

5. The reported² boiling point for 3-phenylpropionaldehyde is 104-105°C (13 mm).

6. The product exhibits the following carbon magnetic resonance spectrum (chloroform-d) δ : 201.4 (d, $\overset{\text{O}}{\text{C}}\text{-H}$), 140.2 (s, ipso), 128.5 (d, meta), 128.2 (d, ortho), 126.1 (d, para), 45.1 (t, $\text{-CH}_2\text{-CHO}$), 27.9 (t, $\text{-CH}_2\text{-CH}_2\text{-CHO}$); ^1H NMR (chloroform-d) δ : 9.80 (t, -CHO), 7.33-7.16 (m, aromatic), 2.95 (m, $\text{-CH}_2\text{-CH}_2\text{-CHO}$), 2.77 (m, $\text{-CH}_2\text{-CHO}$); infrared cm^{-1} : 2700, 1710.

7. (2-Bromoethyl)benzene can be used instead of (2-chloroethyl)benzene; anhydrous diethyl ether is used as the solvent instead of tetrahydrofuran.

3. Discussion

The procedure described here is a one-step conversion of (2-chloroethyl)benzene to 3-phenylpropionaldehyde. The method is general and characterized by good yields, mild conditions, and easy preparation of 3-phenylpropionaldehyde in pure form from readily available starting materials. Several methods are described in the literature for the preparation of 3-phenylpropionaldehyde, including dry distillation of calcium formate with calcium hydrocinnamate,³ sodium amalgam reduction and deprotection of cinnamaldehyde dimethyl acetal,⁴ or formation from heterocyclic system.^{5,6} The present method has been shown⁷ to be applicable to a wide variety of organolithium and Grignard reagents.

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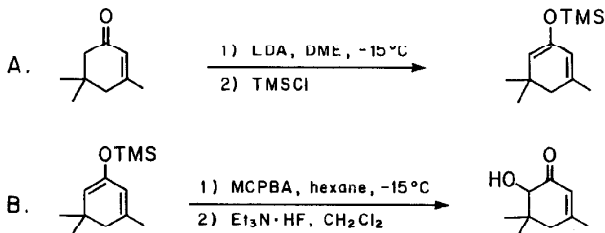
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 3-Phenylpropionaldehyde: Hydrocinnamaldehyde (8); Benzenepropanal (9); (104-53-0)
- (2-Chloroethyl)benzene: Benzene, (2-chloroethyl)- (8,9); (622-24-2)
- N-Formylpiperidine: 1-Piperidinecarboxaldehyde (8,9); (2591-86-8)

WITH *m*-CHLOROPERBENZOIC ACID: 6-HYDROXY-3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE

(2-Cyclohexen-1-one, 6-hydroxy-3,5,5-trimethyl-)



Submitted by George M. Rubottom, John M. Gruber, Henrik D. Juve, Jr.,
and Dan A. Charleson.¹

Checked by Judy Bolton and Ian Fleming.

1. Procedure

A. *4,6,6-Trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene*. A 500-mL, three-necked, round-bottomed flask is fitted with a reflux condenser (center neck), Teflon-covered magnetic stirring bar, ground-glass stopper, and a rubber septum. The apparatus is connected, through the reflux condenser, to a nitrogen source and a bubbler (Note 1). After the flask is flushed with nitrogen, it is charged with 150 mL of dry dimethoxyethane (DME) (Note 2) and 11.25 mL (80.4 mmol) of freshly distilled diisopropylamine (Note 3). The flask is immersed in a methanol-ice bath and cooled to an external temperature of -15°C . Over a period of about 5 min, butyllithium, 49.8 mL (79.6 mmol)

(Note 4), is added, with continuous stirring, with a syringe through the septum. After an additional 15 min of stirring, 10.0 g (72.4 mmol) of freshly distilled isophorone (Note 5) is added neat over a 10-min period. The bright yellow solution is stirred for an additional 10 min at -15°C . At this point, 17.5 mL (137.6 mmol) of freshly distilled chlorotrimethylsilane (TMSCl) (Note 6) is rapidly introduced through the septum. After the addition is complete (ca. 20 sec), the white slurry is stirred for an additional 2 hr at room temperature. The apparatus is then dismantled, the two outside necks of the flask are stoppered with ground-glass stoppers, and the center neck is attached to a rotary evaporator. Solvent is removed under reduced pressure and the residue is treated with 100 mL of pentane. The slurry is filtered through a sintered glass filter and the filtrate is concentrated on a rotary evaporator. The residue is distilled at reduced pressure to give 13.5-13.9 g (88-91%) of pure 4,6,6-trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene, bp $54-57^{\circ}\text{C}$ (1.5 mm), $37-39^{\circ}\text{C}$ (0.01 mm) [lit.² bp $45-49^{\circ}\text{C}$ (0.05 mm)] (Note 7).

B. *6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one*. A 500-mL, three-necked, round-bottomed flask is fitted with an adapter with a stopcock connected to a nitrogen source and a bubbler (center neck), two ground-glass stoppers, and a Teflon-covered magnetic stirring bar (Note 1). After the system is flushed with nitrogen, the flask is charged with 300 mL of dry hexane (Note 8) and 10.0 g (47.5 mmol) of 4,6,6-trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene. The flask is immersed in a methanol-ice bath and cooled to an external temperature of -15°C and then, with stirring, the solution is treated with a slurry which contains 10.6 g (52.3 mmol) of *m*-chloroperbenzoic acid (MCPBA) (Note 9) and 50 mL of dry hexane (Note 10). When the addition is complete (ca. 1.5 min), the resulting slurry is stirred at -15°C for 20 min and then at 30°C (water bath) for 2 hr. The mixture is

filtered through a sintered glass filter into a 500-mL, round-bottomed flask and the solvent is removed under reduced pressure using a rotary evaporator. If solid remains in the residue, 10-15 mL of pentane is added, filtration is repeated, and solvent is again removed under reduced pressure. The flask is fitted with a Teflon-covered stirring bar and the residue is treated with 150 mL of dry methylene chloride (Note 11) and 11.5 g (95.0 mmol) of triethylammonium fluoride (Et_3NHF) (Note 12). After the solution is stirred for 2 hr at room temperature, it is transferred to a separatory funnel and extracted with saturated aqueous sodium bicarbonate solution (2 x 100 mL), 100 mL of 1.5 N hydrochloric acid, and saturated aqueous sodium bicarbonate solution (2 x 50 mL). The organic layer is dried with anhydrous magnesium sulfate, filtered, and solvent is removed from the filtrate using a rotary evaporator. The residue is then freed of the last traces of solvent by pumping, *with stirring*, at reduced pressure (ca. 2.0 mm) (Note 13); the residue solidifies. The round-bottomed flask is attached to a short-path distillation apparatus and the residue is distilled at reduced pressure. After a small forerun, the main fraction, bp 73-75°C (1.3 mm), is collected (Note 14). This fraction solidifies and is triturated with 3-5 mL of petroleum ether (bp 30-60°C) at -15°C (ice-methanol) to remove traces of isophorone. When the crystalline residue is dried in a stream of nitrogen, pure 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one is obtained: 4.8-5.1 g (66-70%), mp 44.5-45°C [lit.³ mp 45-46°C]. The forerun and the material left in the still head after distillation are combined (Note 15) and treated with the petroleum ether that was used to triturate the main fraction. Crystallization gives an additional 0.2-0.3 g (3-4%) of the hydroxy ketone, mp 44.5-45°C. Thus the total weight of the 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one is 5.1-5.4 g (70-73%) (Note 16).

2. Notes

1. All glassware was dried in an oven for 2 hr at 110°C before use. All reactions were carried out under an atmosphere of nitrogen. The checkers used a balloon filled with nitrogen rather than a bubbler.

2. Dimethoxyethane (DME) (Aldrich Chemical Company, Inc.) was dried over lithium aluminum hydride and distilled just before use. The submitters have found that DME is the solvent of choice in this reaction and is preferred over the more commonly used tetrahydrofuran (THF).

3. Diisopropylamine, bp 80-80.5°C (699 mm), (Aldrich Chemical Company, Inc.) was distilled under a static atmosphere of nitrogen just prior to use.

4. Butyllithium (Aldrich Chemical Company, Inc.) was a 1.6 M solution in hexane. The submitters used the method of Ronald⁴ to check titer. It is essential to the success of the reaction that this value be checked with accuracy.

5. Isophorone, bp 85-87°C (10 mm), (Aldrich Chemical Company, Inc.) was distilled immediately before use.

6. Chlorotrimethylsilane (TMSCl), bp 54-55°C (699 mm), (Aldrich Chemical Company, Inc.) was distilled under a static atmosphere of nitrogen just prior to use.

7. The product has the following spectroscopic properties: n_D^{25} 1.4509; infrared (neat) cm^{-1} : 3040 (vinyl CH), 1660 (C=COTMS), 1610 (C=C); ^1H NMR (CDCl_3) δ : 0.21 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.98 (s, 6 H, two CH_3), 1.75 (broad s, 3 H, vinyl CH_3), 1.92 (broad s, 2 H, CH_2), 4.52 (broad s, 1 H, vinyl H on carbon 1), 5.40 (multiplet, 1 H, vinyl H on carbon 3); mass spectrum, m/z (relative abundance using 15 eV): 210 (M^+ , 28), 196 (17), 195 (100), 179 (9); metastable (m^*): 164.3 (195 \rightarrow 179). Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{OSi}$: C, 68.50; H,

10.54. Found: C, 68.50; H, 10.52. A gas chromatographic analysis using a 0.25" x 6.0' column packed with 12.5% SE 52 at a column temperature of 130°C and gas flow rate of 90 mL per minute showed the purity of the product to be greater than 95%. The impurities present were a small amount of unreacted isophorone and a trace of an unidentified material.

8. Hexane was purified in 1.5-L batches by sequential washing with concentrated sulfuric acid (5 x 50 mL) and water (3 x 100 mL), drying (CaCl_2), and distillation. The pure hexane is stored over Linde 4\AA -molecular sieves.

9. m-Chloroperbenzoic acid (MCPBA) (Aldrich Chemical Company, Inc.) containing 15% m-chlorobenzoic acid was obtained commercially and used without purification.

10. It is convenient to stir the 85% MCPBA in hexane while the flask is being charged with the diene. Addition of the slurry with a pipet is the method used by the submitters. The checkers poured it in directly from a beaker, and washed the beaker with 10 mL of hexane.

11. Methylene chloride is dried by distillation from calcium chloride.

12 Triethylammonium fluoride is prepared by the method of Hünig.⁵ The purity of this reagent seems to determine the amount of color that results in the crude hydroxy ketone. Stirring for a period of time greater than 2 hr results in lower yields and is to be avoided.

13. Stirring is crucial to prevent serious bumping when the crude hydroxy ketone solidifies. The checkers simply swirled the flask continuously without incident.

14. Taking a small forerun serves to concentrate residual isophorone in this fraction. Care must also be taken not to overcool the distillation head which may cause crystallization of the hydroxy ketone throughout the system.

15. A small amount of methylene chloride is used to wash the still head. This solvent is then removed (rotary evaporator) prior to the addition of the petroleum ether. Petroleum ether is used if recrystallization is needed.

16. The product has the following spectroscopic properties: infrared (Nujol mull) cm^{-1} : 3360 (OH), 3040 (vinyl CH), 1670, 1635 (C=C-O); ^1H NMR (CDCl_3) δ : 0.79 (s, 3 H, CH_3 on C-5 trans to OH), 1.14 (s, 3 H, CH_3 on C-5 cis to OH), 1.88 (s, 3 H, vinyl CH_3), 2.13 (d, 1 H, $J = 18$, AB doublet for H on C-4), 2.35 (d, 1 H, $J = 18$, AB doublet for H on C-4), 3.52 (d, 1 H, $J = 2$, OH), 3.78 (d, 1 H, $J = 2$, H on C-6), 5.70 (broad s, 1 H, vinyl H); mass spectrum, m/z (relative abundance using 15 eV): 154 (M^+ , 24), 125 (10), 111 (14), 83 (100), 82 (96), 72 (44); metastables (m^*): 101.5 ($154 \rightarrow 125$), 80.0 ($154 \rightarrow 111$). Anal. Calcd for $\text{C}_9\text{H}_{14}\text{O}_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.50. A gas chromatographic analysis using a 0.25" x 6.0' column packed with 12.5% SE-52 at a column temperature of 158°C and a gas flow rate of 90 mL per minute showed the purity of the product to be greater than 98%. In some runs, a trace of isophorone could be detected (ca. 2%).

3. Discussion

The preparation of α -hydroxy carbonyl compounds has been accomplished by the oxidation of enolates using both oxygen⁶ and $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA} \cdot (\text{MoOPh})$.⁷ Acyl anion equivalents offer another route to this useful class of compounds.⁸ The procedure presented here for the synthesis of 6-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one illustrates the use of MCPBA oxidation of an enol silyl ether as a method for obtaining an α -hydroxy enone. The procedure is a scaleup of a published synthesis.⁹

4,6,6-Trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene has been reported by Conia² who used the standard "kinetic method" of House¹⁰ for synthesis of the compound. The current method adapts this synthesis by employing DME as solvent and by using a non-aqueous workup which was previously noted by Ainsworth for the preparation of silyl ketene acetals.¹¹ These changes lead to higher yields of pure enol silyl ethers in general, and are recommended as a standard method.

6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one has been prepared in 22% yield by lead(IV) acetate oxidation of isophorone followed by hydrolysis of the resulting acetate.³ The MCPBA method gives high yields of both α -hydroxy enones¹² and ketones¹³ and is extremely general in scope. The method is also viable for the synthesis of α -hydroxy acids¹⁴ and α -hydroxy esters.¹⁵ The method fails with the enol silyl ethers of both lactones¹⁵ and aldehydes.¹⁶

Since the double bond placement in enol silyl ethers is predictable and controllable,¹³ the method allows the regiospecific introduction of α -hydroxy groups. Omission of the fluoride treatment permits isolation of α -trimethylsiloxy carbonyl compounds,¹⁷ while treatment of enol silyl ethers, first with MCPBA, then with triethylammonium fluoride/acetic anhydride gives the corresponding α -acetoxy carbonyl compounds.⁹ The probable mechanism of the MCPBA oxidation of enol silyl ethers has also been discussed.¹⁸

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

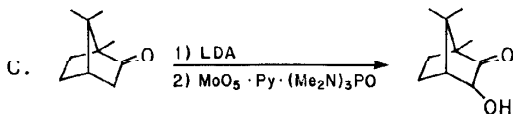
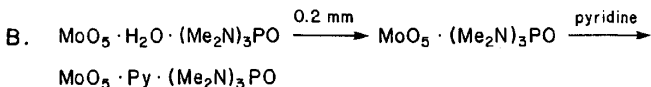
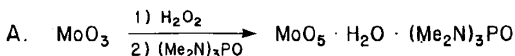
- m-Chloroperbenzoic acid: Peroxybenzoic acid, m-chloro- (8);
Benzenecarboperoxoic acid, 3-chloro- (9); (937-14-4)
- 6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 6-hydroxy-3,5,5-trimethyl- (10); (61592-66-3)
- 4,6,6-Trimethyl-2-trimethylsilyloxycyclohexa-1,3-dione: Silane, trimethyl[(3,3,5-trimethyl-1,5-cyclohexadien-1-yl)oxy]- (9); (54781-28-1)
- Dimethoxyethane: Ethane, 1,2-dimethoxy- (8,9); (110-71-4)
- Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)
- Butyllithium: Lithium, butyl- (8,9); (109-72-8)
- Isophorone: 2-Cyclohexen-1-one, 3,5,5-trimethyl- (8,9); (78-59-1)
- Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)
- Triethylammonium fluoride: Triethylamine hydrofluoride (8);
- Ethanamine, N,N-diethyl-, hydrofluoride (9); (29585-72-6)

HYDROXYLATION OF ENOLATES WITH

OXODIPEROXYMOLYBDENUM(PYRIDINE)(HEXAMETHYLPHOSPHORIC TRIAMIDE),

$\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$ (MoOPH): 1,7,7-TRIMETHYL-3-HYDROXYBICYCLO[2.2.1]HEPTAN-2-ONE

(Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-)



Submitted by Edwin Vedejs and S. Larsen.¹

Checked by Gordon Hill and K. Barry Sharpless.

Caution! Reactions using peroxides should be performed behind a safety shield to minimize explosion hazards (Note 1). Hexamethylphosphoric triamide (HMPA) and methanol are toxic and must be handled in a hood (Note 2).

1. Procedure

A. *Oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide), $\text{MoO}_5 \cdot \text{H}_2\text{O} \cdot \text{HMPA}$.*² A 500-mL, three-necked flask is fitted with an internal thermometer and a mechanical paddle stirrer. The flask is charged, with stirring, with 30 g (0.2 mol) of molybdenum oxide (MoO_3) (Note 3) and 150 mL of 30% hydrogen peroxide (H_2O_2) (Note 4). An oil bath equilibrated at 40°C is

placed under the reaction mixture and heating is continued until the internal temperature reaches 35°C. The heating bath is removed, and replaced by a water bath to control the mildly exothermic reaction so that an internal temperature of 35-40°C is maintained. After the initial exothermic period (approximately 30 min), the reaction flask is placed in the 40°C oil bath and stirred a total of 3.5 hr to form a yellow solution with a small amount of suspended white solid (Note 5).

After cooling to 20°C, the solution is filtered through a 1-cm mat of Celite pressed into a coarse-porosity sintered glass filter. The yellow filtrate is cooled to 10°C (with an ice bath and magnetic stirring) and 37.3 g (0.21 mol) of hexamethylphosphoric triamide (HMPA) (Note 2) is added dropwise over 5 min, resulting in the formation of a yellow crystalline precipitate. Stirring is continued for a total of 15 min at 10°C, and the product is filtered using a Büchner funnel and pressed dry with a spatula. After 30 min in the funnel (aspirator vacuum), the filter cake is transferred to a 1-L Erlenmeyer flask. Methanol (20 mL) is added and the mixture is stirred in the 40°C bath. More methanol is slowly added until the crystals have dissolved. Cooling the saturated solution in the refrigerator gives yellow needles. The crystal mass is broken up with a spatula, the product is filtered, and washed with 20-30 mL of cold methanol to give $\text{MoO}_5 \cdot \text{H}_2\text{O} \cdot \text{HMPA}$, 46-50 g, 59-64% (Notes 5, 6).

B. *Oxidiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$* = MoOPH .² The recrystallized product from above is dried over phosphorus oxide (P_2O_5) in a vacuum desiccator, shielded from the light, for 24 hr at 0.2 mm to give a somewhat hygroscopic yellow solid, $\text{MoO}_5 \cdot \text{HMPA}$. A 36.0-g (0.101 mol) portion of $\text{MoO}_5 \cdot \text{HMPA}$ is dissolved in 150 mL of dry tetrahydrofuran (THF) (Note 7) and the solution is filtered through a Celite

mat, if needed, to remove a small amount of amorphous precipitate. The filtrate is then stirred magnetically in a 20°C water bath while 8.0 g (0.101 mol) of dry pyridine (Note 8) is added over 10 min. The crystalline, yellow product is collected on a Büchner funnel, washed with dry tetrahydrofuran (25 mL) and anhydrous ether (200 mL), and dried in a vacuum desiccator (1 hr, 0.2 mm) to yield 36-38 g (51-53% overall from MoO₃) of finely divided yellow crystalline MoO₅·Py·HMPA (Note 9).

The product is stored in a dark glass jar inside a second container partly filled with Drierite, and the container is kept in the refrigerator. Before opening the jar, the container is allowed to warm to room temperature to avoid condensation of moisture inside. Properly stored MoOPH is a freely flowing crystalline powder and can be used over a period of several months (Note 10).

C. *Hydroxylation of camphor: 1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one.* A solution of lithium diisopropylamide (LDA) is prepared as follows: A 250-mL, three-necked flask and magnetic stirrer are flame dried under a slow stream of nitrogen. After cooling, the flask is charged with 40 mL of approximately 1.5 M butyllithium in hexane (Note 11) under nitrogen flow using a syringe. The flask is cooled in a dry ice-acetone bath and 9.2 mL (66 mmol) of diisopropylamine (Note 8) is added by syringe, followed by 40 mL of dry THF (Note 7). The resulting LDA solution is allowed to reach room temperature under a slow flow of nitrogen. For titration, 0.312 g (2 mmol) of menthol is dissolved in 5 mL of dry THF with a few crystals of phenanthroline (Note 12) under nitrogen flow at -70°C. The LDA solution is added dropwise (using a nitrogen-purged syringe) to the stirred menthol solution until the yellow color of menthoxide-phenanthroline turns to the rust color of LDA - phenanthroline, (2.67 mL of LDA solution is needed, 0.75 M).

An aliquot of 47.1 mL (35.3 mmol) of LDA solution is transferred by nitrogen-filled syringe into a nitrogen-swept, 500-mL, three-necked flask equipped with a magnetic stirrer and a device for addition of solid MoOPH. The latter is an L-shaped glass tube with male joints at each end. A round-bottomed flask containing 20.9 g (48.1 mmol) of MoOPH is wired to the L-tube which is wired to the reaction vessel at such an angle that rotation of the L-tube causes addition of MoOPH to the enolate. The MoOPH container is temporarily suspended using clamps, and the entire apparatus is maintained under a slow flow of nitrogen. After the LDA solution is cooled in a dry ice-acetone bath, 4.88 g (32.1 mmol) of camphor (Note 13) in 200 mL of dry THF is added dropwise with stirring over 0.5 hr. Ten minutes later the reaction is placed in a dry ice - carbon tetrachloride bath and after 15 min the MoOPH is added over 1-2 min by rotating the L-tube and gently tapping to dislodge the powder. The reaction immediately turns orange and eventually fades to a pale tan (Note 14). Stirring is continued at approximately -23°C for 20 min, and the reaction is quenched by adding 100 mL of saturated aqueous sodium sulfite (Na_2SO_3). Vigorous stirring is maintained and the mixture is allowed to warm to room temperature. After 10 min at 20°C , the mixture is shaken with 100 mL of saturated sodium chloride solution, and the aqueous layer is extracted twice with 70 mL of ether. The combined organic layers are washed once with a mixture of 50 mL of 10% aqueous hydrochloric acid and 50 mL of saturated sodium chloride solution. The hydrochloric acid - sodium chloride aqueous layer is back-extracted with 50 mL of ether, the combined organic layers are dried over MgSO_4 , filtered, and evaporated under an aspirator to yield a blue-green oil. Residual molybdenum salts are removed by filtration over 100 g of silica gel (Note 15) in a 2.5-cm column wet-packed and eluted with 1:1 ether-hexane. The product is eluted with approximately 750 mL of ether-hexane.

Evaporation (aspirator) yields a white semi-solid which is crystallized from 15 mL of hexane at -20°C and collected by washing with hexane cooled to -70°C . The mother liquors are crystallized in a similar manner from 2-4 mL of hexane to give a total of five crops, 4.14 g (77%) of colorless needles, mp $170-183^{\circ}\text{C}$, a 5:1 mixture of endo:exo isomers (Note 16). Recrystallization did not affect the isomer ratio (literature mp; endo, $192-195^{\circ}\text{C}$; exo, $210-211^{\circ}\text{C}$).³

2. Notes

1. There are no reports that $\text{MoO}_5 \cdot \text{H}_2\text{O} \cdot \text{HMPA}$, $\text{MoO}_5 \cdot \text{HMPA}$, or $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$ are shock-sensitive. Upon heating on a hot plate, the crystalline solids ignite and burn, but do not detonate. These compounds can be stored in a refrigerator with precautions to exclude light. Prolonged storage at room temperature in the light may cause decomposition with gas evolution and an exotherm sufficient to crack a glass container.

2. Hexamethylphosphoric triamide is toxic and a cancer-suspect agent.

3. Molybdenum oxide was obtained from Mallinckrodt Inc.

4. Hydrogen peroxide was obtained from Mallinckrodt Inc.

5. Failure to maintain the internal temperature below 40°C results in formation of amorphous, insoluble products.

6. The purity of this material is decisive because the quality of subsequent products cannot be improved by recrystallization because of some decomposition.

7. Tetrahydrofuran was distilled from sodium-benzophenone and stored under nitrogen.

8. Pyridine was distilled from barium oxide.

9. The product melts with vigorous evolution of gas at $103-105^{\circ}\text{C}$.

10. Prolonged exposure to light, or failure to control exothermic reactions in prior steps, results in a sticky product which smells of pyridine. No method for purifying partly decomposed MoOPH has been found, and "sticky" product should not be used for enolate hydroxylation. Suspect material can be decomposed by stirring with aqueous sodium sulfite (Na_2SO_3) solution.

11. Butyllithium was obtained from the Foote Mineral Company.

12. Menthol and phenanthroline were obtained from the Aldrich Chemical Company, Inc.

13. Camphor was obtained from Eastman Organic Chemicals.

14. The colors are somewhat substrate dependent. Some enolate hydroxylations acquire a green-blue color.

15. Silica gel, 60-200 mesh, was obtained from Davison Chemical Division.

16. The endo:exo ratio is determined by comparing the NMR CHOH signal areas of the endo (4.21 ppm, d, $J = 4.8$ Hz) and exo (3.75 ppm, br s) isomers.

3. Discussion

Enolate hydroxylation is a problem of long standing. Direct oxygenation succeeds with the fully substituted enolates of certain α,α -disubstituted ketones⁴ and a variety of carboxylic acid derivatives (ester anions, acid dianions, amide anions),⁵ but the reaction of enolates, $\text{RCH} = \text{C}(\text{O}^-)\text{R}'$ or $\text{CH}_2 = \text{C}(\text{O}^-)\text{R}'$, with oxygen results in complex products of overoxidation. The stable molybdenum peroxide reagent $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPA}$ (MoOPH),² first prepared by Mimoun, allows the conversion of $\text{RCH} = \text{C}(\text{OLi})\text{R}'$ into $\text{RCH}(\text{OH})\text{COR}'$ in generally good yields (Table I).⁶ In some cases, the α -diketone is formed as a byproduct.


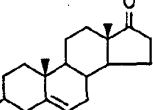
The MoOPH reagent also hydroxylates branched or unbranched ester, amide, and nitrile anions.^{6,7} For unknown reasons, MoOPH hydroxylations often do not give complete conversion of enolates into products, and recovery of 5-15% of the starting carbonyl substrate is to be expected.

Methyl ketone enolates are hydroxylated by MoOPH, but the products tend to undergo condensation with the starting enolate, resulting in poor yields.⁶ Methyl ketone hydroxylation has been described by Moriarty, using $\text{C}_6\text{H}_5\text{I}=\text{O}/\text{CH}_3\text{OH}-\text{OH}^\ominus$.⁸

Several indirect methods for conversion of enolates into α -hydroxycarbonyl compounds are known. The most versatile is the reaction of enol silanes with meta-chloroperbenzoic acid developed by Rubottom.⁹ This technique is often successful with substrates which are oxidized inefficiently by the MoOPH technique.

The method described for MoOPH hydroxylation of the camphor enolate is representative for ketone enolate hydroxylations, but optimization in each individual case to determine the best temperature and concentration is recommended. Large scale oxidations may benefit from addition of reagent in several portions over time, and enolates which are sensitive to self-condensation may give higher yields if enolate is added slowly to excess MoOPH.

TABLE I

Ketone	Oxidation temp. (°C)	α -Hydroxy ketone	α -Diketone
valerophenone	-22 -44	60 % 62 %	13% < 2%
deoxybenzoin	-44	34 %	26%
isobutyrophenone	-22	65 %	
α -tetralone	-22	48 %	
camphor	-22 -22 \rightarrow 60, 16 hr	77 % 44 %	< 2 % 11%
4,4-diphenyl- cyclohexanone	-22	46 %	
2-phenylcyclohexanone	-44	70 %	< 5%
	-22	81%	
	-44	75 % (16 α -OH)	

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Oxidoperoxymolybdenum(pyridine)(hexamethylphosphoric triamide): Molybdenum, (hexamethylphosphoric triamide)oxidiperoxy(pyridine)- (8,9); (23319-63-3)
1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one: Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl- (9); (10373-81-6)
endo-1,7,7-Trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one: Bicyclo[2.2.1]heptan-2-one, 3-hydroxy-1,7,7-trimethyl-, endo- (9); (21488-68-6)
Hexamethylphosphoric triamide: Phosphoric triamide, hexamethyl- (8,9); (680-31-9)
Oxidoperoxymolybdenum(aqua)(hexamethylphosphoric triamide): Molybdenum, aqua(hexamethylphosphoric triamide)oxidiperoxy- (8,9); (23319-56-4)
Molybdenum oxide (8,9); (1313-27-5)
Hydrogen peroxide (8,9); (7722-84-1)
Phosphorus oxide (8,9); (1314-56-3)
Pyridine (8,9); (110-86-1)
Oxidoperoxymolybdenum(hexamethylphosphoric triamide): Molybdenum, (hexamethylphosphoric triamide)oxidiperoxy- (8); Molybdenum, (hexamethylphosphoric triamide-0)oxidiperoxy- (9); (25377-12-2)
Camphor (8); Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl- (9); (76-22-2)
Lithium diisopropylamide: Diisopropylamine, lithium salt (8);
2-Propanamine, N-(1-methylethyl)-, lithium salt (9); (4111-54-0)
Butyllithium: Lithium, butyl- (8,9); (109-72-8)
Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Menthol (8); Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1 α , 2 β , 5 α)- (9); (89-78-1)

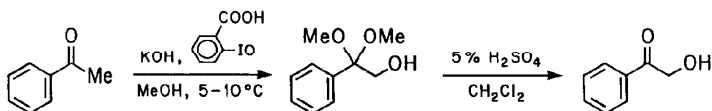
Phenanthroline: 1,10-Phenanthroline (8,9); (66-71-7)

Sodium sulfite: Sulfurous acid, disodium salt (8,9), (7757-83-7)

α -HYDROXYLATION OF A KETONE USING o-IODOSYLBENZOIC ACID:

α -HYDROXYACETOPHENONE VIA THE α -HYDROXY DIMETHYLACETAL

(Ethanone, 2-hydroxy-1-phenyl-)



Submitted by Robert M. Moriarty, Kwang-Chung Hou, Indra Prakash,
and S. K. Arora.¹

Checked by Janice Klunder and K. Barry Sharpless.

1. Procedure

A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, 100-mL pressure-equalized addition funnel to which is attached a drying tube, and a stopper. Anhydrous methanol (80 mL) (Note 1) is added to the flask, which is cooled to 5–10°C. Stirring is begun and 8.4 g (0.15 mol) of powdered potassium hydroxide is added. Acetophenone (6.0 g; 0.05 mol) (Note 2) dissolved in 20 mL of methanol is added dropwise over a period of 10 min. After the solution is stirred for 15 min, 14.52 g (0.055 mol) of *o*-iodosylbenzoic acid (Note 3) is added during 30 min. The ice bath is removed and the resultant yellow-colored slurry is stirred overnight at room temperature to give a clear red solution (Note 4). The mixture is concentrated under reduced pressure in a rotary evaporator, until one-half of the methanol is removed, then 30 mL of water is added followed by extraction

with four 50-mL portions of dichloromethane. The combined dichloromethane extracts are washed with two 10-mL portions of water, and the combined organic extracts are dried over anhydrous magnesium sulfate for 1 hr. After filtration, the methylene chloride is removed under reduced pressure in a rotary evaporator, and the crude acetal is distilled to give a fraction at 73-76°C (0.4 mm) which weighs 6.0 g (65%) (Note 5). The acetal is of high purity, as shown by spectral analysis (Note 6).

α-Hydroxyacetophenone. In a 500-mL, round-bottomed flask equipped with a magnetic stirrer are placed 6.0 g (0.33 mol) of α -hydroxy dimethylacetal and 100 mL of dichloromethane. Stirring is begun and the flask is cooled to about 10°C with ice water. Aqueous 5% sulfuric acid (100 mL) is added dropwise from a pressure-equalized addition funnel and the mixture is stirred for another 30 min. The dichloromethane layer is separated and the aqueous layer is extracted twice with 25-mL portions of dichloromethane. The combined extracts are washed with two 10-mL portions of water, dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure using a rotary evaporator. The resulting yellow crystalline solid is recrystallized from carbon tetrachloride to give a white crystalline material, mp 86-87.5°C (lit.² mp 86-87°C), yield 3.7 g (83%) (Note 7).

2. Notes

1. Anhydrous methanol is obtained by treatment with magnesium methoxide, obtained by refluxing 50 mL of methanol, 5 g of magnesium turnings, and 0.5 g of sublimed iodine together until the iodine color disappears. Then 1 L of methanol is added and the system is kept at reflux for 1 hr and distilled to yield purified methanol (bp 64.5°C).

2. Acetophenone was used as purchased from Fisher Scientific Company.

3. o-Iodosylbenzoic acid was used as purchased from Sigma Chemical Company.

4. TLC (ethyl acetate:hexane) shows residual starting material.

5. The α -hydroxy dimethylacetal obtained must be used immediately in the next step because at room temperature it undergoes a dimerization reaction by loss of two molecules of methanol.

6. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 3470 (-OH); ^1H NMR (CDCl_3) δ : 1.83 (s, 1 H, OH), 3.23 (s, 6 H, $(\text{OCH}_3)_2$), 3.73 (s, 2 H, CH_2), 7.27-7.67 (m, 5 H, Ar H); ^{13}C NMR (CDCl_3) δ : 139.3 (s), 129.4 (d), 127.4, (d) 102.4 (s), 65.3 (t) 49.1 (q); mass spectrum: m/e 151 ($\text{M}^+ - \text{OCH}_3$ 100%), 105 (29.7%), 91 (31.7%), 77 (7.0%).

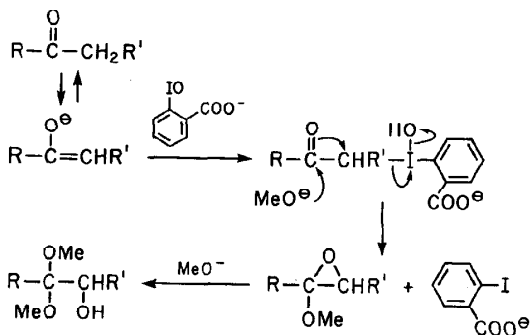
7. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 3.63 (s, 1 H, OH), 4.86 (s, 2 H, CH_2), 7.25-7.90 (m, 5 H, Ar H); ^{13}C NMR (CDCl_3) δ : 198.6 (s), 134.4 (s), 129.1 (d), 127.8 (d), 65.6 (t).

3. Discussion

The procedure reported here provides a convenient method for the α -hydroxylation of ketones which form enolates under the reaction conditions. The reaction has been applied successfully to a series of para-substituted acetophenones, 1-phenyl-1-propanone, 3-pentanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclododecanone, 2-methylcyclohexanone, 2-norbornanone and benzalacetone.³ In the case of a steroidal example it was shown that a carbon-carbon double bond and a secondary hydroxyl group are not oxidized.⁴ A primary amino function, as in the case of p-aminoacetophenone, is not affected.⁵ Similarly, a tertiary amino ketone such as tropinone undergoes the α -hydroxylation reaction.⁵

The present procedure using o-iodosylbenzoic acid is an improvement over our original method which uses either iodosylbenzene or diacetoxyphenyliodine(III).^{6,7,8} The advantage of the present method is the solubility of the product iodobenzoic acid under the basic reaction conditions. Thus the α -hydroxy dimethylacetal may be isolated by direct extraction. Using the original procedure both carboxylic acids and esters underwent high yield α -hydroxylation.⁸

The pathway by which the reactions are considered to occur involves attack of the enolate anion at the I=O bond of o-iodosylbenzoic acid followed by reductive elimination of o-iodobenzoic acid upon addition of methoxide to the carbonyl group. Ring opening of the epoxide thus formed yields the hydroxy dimethylacetal:



Other methods for α -hydroxy ketone synthesis are: addition of $^3\text{O}_2$ to an enolate followed by reduction of the α -hydroperoxy ketone using triethyl phosphite;⁹ the molybdenum peroxide-pyridine-HMPA oxidation of enolates;¹⁰ photooxygenation of enol ethers followed by triphenylphosphine reduction;¹¹ the epoxidation of trimethylsilyl enol ethers by peracid;¹² the oxidation of trimethylsilyl enol ethers by osmium tetroxide in N-methylmorpholine N-oxide;¹³ and finally the classical method of hydrolysis of an α -bromo ketone.¹⁴

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

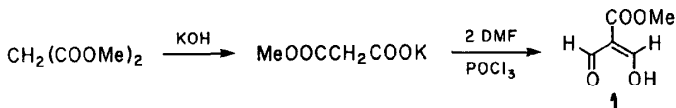
o-Iodosylbenzoic acid: Benzoic acid, *o*-iodoso- (8); Benzoic acid, 2-iodosyl- (9); (304-91-6)

α -Hydroxyacetophenone: Acetophenone, 2-hydroxy- (8); Ethanone, 2-hydroxy-1-phenyl- (9); (582-24-1)

Acetophenone (8); Ethanone, 1-phenyl- (9); (98-86-2)

α -Hydroxyacetophenone dimethyl acetal: Acetophenone, 2-hydroxy-, dimethyl acetal (8,9); (28203-05-6)

METHYL DIFORMYLACETATE



Submitted by C. R. Hutchinson, M. Nakane, H. Gollman,
and P. L. Knutson.¹

Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

4. *Potassium monomethyl malonate.* Dimethyl malonate (Note 1, 264.2 g, 2.0 mol) is dissolved in anhydrous methanol (Note 2, 1150 mL) contained in a dry, 3-L, one-necked flask containing a large magnetic stirring bar and protected from atmospheric moisture with a calcium sulfate-filled drying tube. The solution is stirred magnetically and cooled to ice-water bath temperature. Potassium hydroxide pellets (112.2 g, 2.0 mol) are added rapidly to the cold solution and the reaction mixture is allowed to warm to room temperature with stirring overnight. The colorless crystals of potassium monomethyl malonate which form are recovered by suction filtration through a Buchner funnel and washed with anhydrous diethyl ether. The combined filtrate and diethyl ether wash are concentrated at 30°C to a volume of ca. 750 mL on a rotary evaporator. The resulting crystalline precipitate is recovered as before by filtration and washing and combined with the first crop of crystals

to give 220 g (71%) of potassium monomethyl malonate as fine colorless needles, mp 204-207°C. These crystals are dried under vacuum (0.1 mm) before use in the following reaction.

B. *Methyl diformylacetate*. Freshly distilled phosphorus oxychloride (612 g, 4 mol) is added dropwise with constant stirring at ambient temperature (Note 3) to dimethylformamide (1460 g) contained in a 3-L. three-necked flask equipped with a mechanical paddle stirrer, immersion thermometer, and a 500-mL pressure-equalizing addition funnel fitted with a calcium chloride-filled drying tube. The reaction mixture warms up and turns to a dark reddish-brown color during addition of the phosphorus oxychloride and formation of the Vilsmeier reagent $[(CH_3)_2N=CHCl \ Cl^-]$. The addition funnel is replaced with a 10-inch long West condenser (Note 4) and then the reaction mixture is cooled to 0°C by immersing the reaction flask in an ice-salt water bath. The cooling bath is removed and potassium monomethyl malonate (206 g, 1.32 mol) is added to the stirred reaction mixture in ten equal portions over a thirty-minute period (Notes 3, 5), keeping the temperature of the mixture below 90°C. The dark brown mixture then is stirred and heated on a water bath at 90°C for 4 hr. Gas (CO₂ plus HCl) evolves initially from the reaction upon heating (Note 6). The thermometer is replaced with a glass stopper, the condenser is fixed for distillation by addition of a distilling head and vacuum distillation receiver, and the reaction solvent is removed from the reaction flask by distillation at ca. 2 mm on a steam bath (Note 7). The resulting dark brown liquid is poured onto ice (4 kg. Note 3). A saturated aqueous solution of potassium carbonate (1.3 kg) is added slowly to the ice-cold crude reaction product with constant stirring until the pH of the mixture stabilizes at ca. 11. Considerable foaming and gas evolution (CO₂) occur during the addition of the base. The resulting basic solution is stirred magnetically at ambient

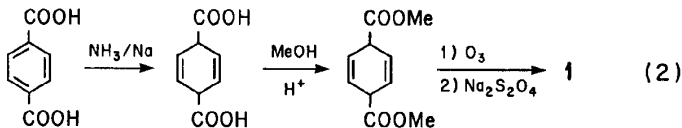
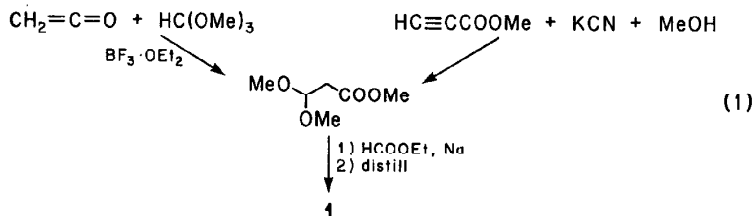
temperature for 48 hr and then extracted with ethyl acetate in four 1-L portions. The organic phases are discarded, and the aqueous phase is saturated with potassium chloride (500 g) by stirring at ambient temperature until no more salt dissolves. This mixture is mixed with ice (1 kg), slowly acidified to pH 1 with ice-cold 12 N hydrochloric acid, and then thoroughly extracted with four 2-L portions of diethyl ether (Note 8). The combined cold ether extracts are washed with a saturated aqueous solution of potassium chloride (4 L) and dried over anhydrous sodium sulfate (500 g) for 1 hr. The solution is decanted from the desiccant, combined with a 500-mL diethyl ether wash of the desiccant, concentrated under reduced pressure to ca. 500 mL, and redried over anhydrous sodium sulfate. After removal of the desiccant by gravity filtration, the diethyl ether is removed by rotary evaporation at water aspirator pressure and 25°C. Fractional distillation of the resulting liquid residue at 2 mm with a N₂ bleed capillary through a Claisen head first gives a little dimethylformamide. When dimethylformamide ceases to distill (Note 9), the receiver is cooled in a dry ice-ethanol bath and the methyl diformylacetate distilled at 58-61°C to give 86-94 g (50-55%) of a colorless, solid distillate, which melts at about 10°C (Notes 10, 11). Methyl diformylacetate prepared in this way is stable for at least 6 months if stored at -20°C.

2. Notes

1. All reagents are used as received from commercial suppliers unless stated otherwise.
2. Reagent grade methanol is made anhydrous by refluxing over $\text{Mg}(\text{OCH}_3)_2$ according to the method of Vogel.²
3. All of the following operations must be done in a hood.
4. The desiccant in the drying tube should be replaced with fresh calcium chloride and the drying tube fitted onto the top of the condenser.
5. The salt is added by replacing the condenser with a glass powder funnel, quickly pouring the crystalline solid through the funnel into the flask, and then replacing the powder funnel with the condenser.
6. The condenser can be cooled to prevent loss of solvent that is carried out of the reaction mixture by the escaping gases.
7. The volume of dimethylformamide distillate is ca. 1000 mL, and distillation is stopped when no more liquid distills from the reaction mixture.
8. The solvent extractions and washings should be done as rapidly as is possible since the crude methyl diformylacetate is not stable to small amounts of acid or base over long periods.
9. Dimethylformamide ceases to distill at a temperature less than 30°C.
10. Considerable product is lost if the receiver is not chilled to a low temperature.
11. The submitters have obtained the same yield when this procedure was done on scales from 0.5 to 1.3 mol.

3. Discussion

Methyl diformylacetate can be prepared from ketene and trimethyl orthoformate,³ or methyl propiolate and methanol,⁴ via formylation of the methyl 3,3-dimethoxypropanoate intermediate (eq. 1). The present procedure is better because it avoids the tedious preparation of ketene,³ affords a superior yield,³ or is much cheaper⁴ than the other two methods. A fourth method⁵ for its preparation (eq. 2) should permit the preparation of any ester of diformylacetic acid that is stable to Birch reduction and ozonolysis conditions. However, this method is not convenient for use above a 0.1-mole scale, nor recommended for reasons of safety because of the amount of an O_2/O_3 mixture needed at larger scales.



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

Methyl diformylacetate: 2-Propenoic acid, 2-formyl-3-hydroxy-, methyl ester (9); (39947-70-1)

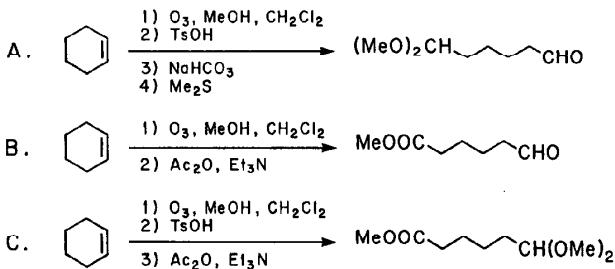
Potassium monomethyl malonate: Propanedioic acid, monomethyl ester, potassium salt (9); (38330-80-2)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

Phosphorus oxychloride: Phosphoryl chloride (8,9); (10025-87-3)

Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)

OZONOLYTIC CLEAVAGE OF CYCLOHEXENE TO TERMINALLY DIFFERENTIATED PRODUCTS:
METHYL 6-OXOHEXANOATE, 6,6-DIMETHOXYHEXANAL, METHYL 6,6-DIMETHOXYHEXANOATE
(Hexanoic acid, 6-oxo-, methyl ester; Hexanal, 6,6-dimethoxy-;
Hexanoic acid, 6,6-dimethoxy-, methyl ester)



Submitted by Ronald E. Claus and Stuart L. Schreiber.¹

Checked by Nakcheol Jeong and Martin F. Semmelhack.

1. Procedure

Caution! The ozonolysis reaction produces peroxidic intermediates which can present a potential explosion hazard. Accordingly, it is recommended that the following experiments be carried out in a hood and behind a safety shield.

A. A 500 mL, three-necked, round-bottomed flask is fitted with a glass tube to admit ozone, a calcium chloride drying tube, a glass stopper, and a magnetic stirring bar and is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, and 50 mL of methanol (Note 1). The flask is cooled to ca. -78°C (2-propanol/dry ice) and ozone (Note 2) is bubbled through

the solution with stirring. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The drying tube and ozone inlet are replaced with a stopper and rubber septum, and 1.215 g of p-toluenesulfonic acid (TsOH) (10% w/w) (Note 4) is added. The solution is allowed to warm to room temperature as it stirs under an atmosphere of nitrogen for 90 min. Anhydrous sodium bicarbonate (2.147 g, 4 mol-equiv) is added to the flask and the mixture is stirred for 15 min, and then 12 mL of dimethyl sulfide (0.150 mol) (Note 5) is added. After being stirred for 12 hr, the heterogeneous mixture is concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (100 mL) is added and the mixture is washed with 75 mL of water (Note 6). The aqueous layer is extracted with two more 100-mL portions of dichloromethane, and the combined organic layers are washed with 100 mL of water. After extracting the aqueous layer with 100 mL of dichloromethane, the organic layers are dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. Short path distillation of the crude product (Note 7) gives 8.2-8.4 g of 6,6-dimethoxyhexanal, 68-70%, bp 80-82°C/1.75 mm (Notes 8 and 9).

B. A round-bottomed flask equipped as in Procedure A is charged with 6.161 g of cyclohexene (0.075 mol), 250 mL of dichloromethane, 50 mL of methanol, and 2.0 g of anhydrous sodium bicarbonate (Notes 1 and 10). After the apparatus is cooled to ca. -78°C, ozone (Note 2) is bubbled through the solution as it is stirred. Ozone addition is stopped when the solution turns blue. Nitrogen is passed through the solution until the blue color is discharged (Note 3) and then the cold bath is removed. The solution is filtered into a 1-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation (Note 11).

After dilution with 225 mL of dichloromethane the flask is cooled to 0°C and 16 mL of triethylamine (0.113 mol) and 21.24 mL of acetic anhydride (0.225 mol) are added via syringe (Note 12), and the solution is stirred under a nitrogen atmosphere for 15 min. The ice bath is removed and stirring is continued for 4 hr. The solution is washed with 150-mL portions of aqueous 0.1 N hydrochloric acid, aqueous 10% sodium hydroxide, and water. The organic layer is dried over anhydrous magnesium sulfate, filtered, and the solvent is removed by rotary evaporation. Short path distillation of the crude product yields methyl 6-oxohexanoate, (7.0-7.8 g, 65-72%), bp 83-86°C/1.5 mm (Note 13).

C. Cyclohexene, 6.161 g (0.075 mol), is stirred with ozone in dichloromethane and methanol, as above. The resulting solution is treated with p-toluenesulfonic acid and subsequently neutralized with sodium bicarbonate, as described in Procedure A. The solution is filtered into a 1-L, round-bottomed flask, 80 mL of benzene is added, and the volume is reduced to approximately 50 mL by rotary evaporation (Note 11). Dilution with dichloromethane, treatment with triethylamine and acetic anhydride, and workup as described in Procedure B followed by short path distillation provides methyl (6,6-dimethoxy)hexanoate, (11.2-11.8 g, 78-83%), bp 87-91°C/1.5 mm (Note 14).

2. Notes

1. Cyclohexene was purchased from Aldrich Chemical Company, Inc. and used without purification. Dichloromethane was distilled from calcium hydride. Methanol was distilled from magnesium.

2. Ozone was produced by a Welsbach Corporation Ozonator, style T-709, with the voltage set at 100 volts and oxygen pressure at 7 p.s.i. to give approximately 2% ozone concentration. The input oxygen was passed through a column of Hammond Drierite to ensure dryness.

3. The blue color indicates that cleavage of the olefin is complete. Excess ozone is removed to prevent over-oxidation.

4. Although the ozonolysis product exists in oligomeric form, the amount of acid used was calculated by assuming a theoretical yield of the corresponding monomeric aldehyde--methoxy hydroperoxide. p-Toluenesulfonic acid monohydrate, purchased from Aldrich Chemical Company, Inc., was not further purified.

5. The solution is neutralized to prevent bisacetal formation upon subsequent reduction. Dimethyl sulfide was purchased from Aldrich Chemical Company, Inc. and used without purification.

6. An aqueous workup facilitates the removal of dimethyl sulfoxide produced by the reduction of the peroxide.

7. Typically 12.4-13.0 g of crude product is obtained after solvent removal. Material of this quality is satisfactory for most subsequent reactions.

8. The distilled product is similar in purity to the crude material. A small amount of dimethyl sulfoxide and minor impurities remain. Purification of the crude product by flash chromatography (1:1 ether/hexanes) affords 6,6-dimethoxyhexanal that is pure by ^1H and ^{13}C NMR in 90-95% yield.

9. The following spectral properties of the product were observed: ^1H NMR (CDCl_3), δ : 9.7 (t, 1 H, $J = 2.5$), 4.3 (t, 1 H, $J = 5.3$), 3.3 (s, 6 H), 2.4 (t, 2 H, $J = 7$), 1.4-1.7 (m, 6 H). ^{13}C NMR (CDCl_3), ppm: 201.6, 103.9, 52.1, 43.2, 31.8, 23.7, 21.4 IR (film), cm^{-1} : 2700, 1720, 1100. MS, m/e (rel %): 113(95), 57(100).

10. Sodium bicarbonate serves to buffer the solution and prevent acetal formation.

11. Benzene is added to facilitate the removal of methanol. Although an aqueous wash will remove the methanol, azeotropic removal with benzene is simpler and provides a slightly higher yield.

12. Triethylamine, purchased from Aldrich Chemical Company, Inc., was distilled from calcium hydride. Acetic anhydride as supplied by Mallinckrodt, Inc. was distilled from phosphorus pentoxide.

13. The following spectral properties were observed: ^1H NMR (CDCl_3), δ : 9.7 (t, 1 H, $J = 2.5$), 3.6 (s, 3 H), 2.2-2.4 (m, 4 H), 1.5-1.7 (m, 4 H). ^{13}C NMR (CDCl_3), ppm: 201.4, 173.1, 51.0, 42.9, 33.2, 24.0, 21.1. IR (film), cm^{-1} : 2700, 1720, 1150. MS: m/e (rel. %): 159(1), 29(3), 75(100).

14. The following spectral properties were observed: ^1H NMR (CDCl_3), δ : 4.25 (t, 1 H, $J = 5.5$), 3.6 (s, 3 H), 3.2 (s, 6 H), 2.15 (t, 2 H, $J = 8$), 1.0-1.6 (m, 6 H). ^{13}C NMR (CDCl_3), ppm: 173.1, 103.9, 52.0, 50.7, 33.4, 31.8, 24.3, 23.7. IR (film), cm^{-1} : 1735, 1050, MS: m/e (rel. %): 159(10), 127(30), 75(100).

3. Discussion

This procedure illustrates a recently published method for the ozonolytic cleavage of cycloalkenes to terminally differentiated products.² Other examples of the unsymmetrical cleavage of olefins have been reported.³ In addition, the title compounds have been prepared by other routes. Methyl 6-oxohexanoate has been synthesized from the acid chloride or the half ester of adipic acid.⁴ It has also been prepared from ϵ -caprolactone by methanolysis followed by oxidation.⁴ Lead tetraacetate treatment of 2-hydroxycyclohexanone in methanol and subsequent acidification produces methyl 6,6-dimethoxyhexanoate.⁵ A three step route from cyclohexanone enol acetate

(ozonolysis in methanol, reaction with dimethyl sulfide, then with trimethyl orthoformate) has been reported.⁶ 6,6-Dimethoxyhexanal has been made by a multistep route.⁷

The present method utilizes commercially available cycloalkenes and proceeds under mild conditions to provide synthetically useful products. The method was shown to be general in the series of cycloalkenes investigated. Yields range from moderate (cyclopentene) to excellent (higher homologues).

The ozonolytic cleavage of cycloalkenes in the presence of methanol produces a chain with an aldehyde and a methoxy hydroperoxide group at the termini.⁸ The unsymmetrical ozonolysis product is manipulated in several ways. Dehydration of the methoxy hydroperoxide group affords an ester (Procedure B). Alternatively, the aldehyde moiety is protected as an acetal. Under these conditions, the methoxy hydroperoxide is reduced⁹ (Procedure A) or dehydrated (Procedure C).

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclohexene (8,9); (110-83-8)

Methyl 6-oxohexanoate: Hexanoic acid, 6-oxo-, methyl ester (9); (6654-36-0)

6,6-Dimethoxyhexanal: Hexanal, 6,6-dimethoxy- (9); (55489-11-7)

Methyl 6,6-dimethoxyhexanoate: Hexanoic acid, 6,6-dimethoxy-, methyl ester (9); (25176-55-0)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl- (9); (104-15-4)

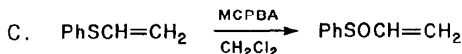
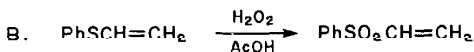
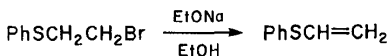
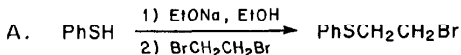
Dimethyl sulfide: Methyl sulfide (8); Methan, thiobis- (9); (75-18-3)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

PHENYL VINYL SULFONE AND SULFOXIDE

(Benzene, (ethenylsulfonyl)- and benzene, (ethenylsulfiny)-)



Submitted by Leo A. Paquette and Richard V. C. Carr.¹

Checked by Wayne Schnatter and Martin F. Semmelhack.

1. Procedure

Caution! 1-Phenylthio-2-bromoethane is a powerful alkylating agent which causes severe skin blistering. Although the present one-pot procedure eliminates the cumbersome handling of this intermediate, due care must be exercised to avoid exposure to this substance.

A. Phenyl vinyl sulfide. In a 1-L, three-necked, round-bottomed flask fitted with magnetic stirrer, condenser, addition funnel, and nitrogen inlet tube is placed 400 ml of ethanol. Sodium metal (23 g, 1 g-atom), cut into small pieces, is added with stirring. When conversion to sodium ethoxide is

complete (5-15 min), the stopper of the addition funnel is removed under a positive flow of nitrogen, and benzenethiol (110 g, 1 mol) is poured into the addition funnel. The stopper is put in place, and the benzenethiol is added over 15-20 min to the cloudy, gray sodium ethoxide solution. The reaction mixture warms spontaneously and becomes clear brown. At 25°C this solution is transferred by stainless steel cannula (Note 1) over 45 min to a stirred solution of 1,2-dibromoethane (272 g, 1.45 mol) in ethanol (28 mL) contained in a 2-L, three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, reflux condenser, nitrogen inlet tube, and internal thermometer (Note 2). The reaction temperature is maintained at 25-30°C by cooling with an ice bath. The mixture is stirred under nitrogen for 30 min and treated for an additional 30 min with ethanolic sodium ethoxide prepared from 40 g (2.17 g-atom) of sodium and 800 mL of ethanol (Note 3). The resulting mixture is stirred at the reflux for 8 hr (Note 4), cooled, and treated with 750 mL of benzene and 750 mL of water. The organic layer is separated, washed with water (2 x 50 mL) and brine (100 mL), and concentrated by rotary evaporation. The yellow oil which results is distilled to give 70-87 g (50-65%) of phenyl vinyl sulfide, bp 91-93°C/20 mm (Notes 5, 6).

B. Phenyl vinyl sulfone. In a 250-mL, three-necked, round-bottomed flask fitted with a magnetic stirrer, condenser, addition funnel, and thermometer is placed 19.7 g (0.145 mol) of phenyl vinyl sulfide dissolved in 70 mL of glacial acetic acid. Hydrogen peroxide (30%, 56 mL, 0.5 mol) is added slowly at such a rate to maintain a reaction temperature of 70°C (Note 7). The reaction mixture is heated at reflux for 20 min, cooled, and treated with ether (150 mL) and water (200 mL). The organic phase is separated, washed with water (50 mL) and brine (50 mL), and concentrated at 70°C/0.3 mm for 3 hr, to afford 18-19 g (74-78%) of phenyl vinyl sulfone as a colorless

solid, mp 64-65°C. Although this material is sufficiently pure for most purposes, recrystallization from hexane affords colorless crystals, mp 66-67°C (Note 8).

C. *Phenyl vinyl sulfoxide*. A 500 mL, three-necked, round-bottomed flask equipped with a dropping funnel and magnetic stirrer is charged with 20 g (0.147 mol) of phenyl vinyl sulfide and 250 mL of dichloromethane. The solution is stirred and cooled to -78°C while a solution of m-chloroperbenzoic acid (25.4 g, 1.0 equiv) in 200 mL of dichloromethane is added dropwise during a 30-min period. The mixture is stirred and warmed to room temperature for 1 hr in a water bath at 30°C. The mixture is then poured into 300 mL of saturated sodium bicarbonate solution, and the mixture is extracted with three 250-mL portions of dichloromethane. The combined organic extracts are washed with three 250-mL portions of water and dried over anhydrous magnesium sulfate. The solvent is removed by rotary evaporation and the residual liquid is distilled to afford 15-16 g (68-70%) of phenyl vinyl sulfoxide as a colorless liquid, bp 98°C/0.6 mm (Notes 9 and 10).

2. Notes

1. The cannula is a stainless steel tube, 16 gauge, sharpened to a needle at both ends, and 60 cm long. One end is placed through a rubber septum into the flask containing the 1,2-dibromoethane solution, while the other end is positioned under the surface of the benzenethiolate solution. Control of the nitrogen pressure allows slow transfer of the benzenethiolate solution.

2. The yield in the previously published method for the preparation of this sulfide is low, affording chiefly 1,2-bis(phenylthio)ethane.² The problem is overcome here by utilization of an inverse addition procedure.

3. Alternatively, dry, powdered sodium ethoxide may be substituted with a corresponding reduction of the reaction volume.

4. Thin layer chromatographic analysis at this stage shows that 1-phenylthio-2-bromoethane is absent.

5. This product has the following spectral properties: IR (neat) cm^{-1} : 3040, 1585, 1475, 1435, 1085, 1020, 950, 735, and 680; ^1H NMR (chloroform- d) δ : 5.25 (superimposed doublets, 2 H, $J = 12$ and 18, terminal vinyl), 6.50 (dd, 1 H, $J = 12$ and 18, olefinic), 7.32 (m, 5 H, aromatic).

6. When stored at room temperature, phenyl vinyl sulfide becomes yellow-colored within 1 day and a black syrup after 1 week. This decomposition can be substantially retarded by storage under a nitrogen or argon atmosphere in a freezer.

7. The submitter observed the temperature increase to 70°C during addition of the first 10 mL of hydrogen peroxide. The checkers noted that the mixture never rose in temperature to 70°C .

8. This product has the following spectral properties: IR (CHCl_3) cm^{-1} : 3020, 1445, 1380, 1315, 1145, 1080, and 965; ^1H NMR (chloroform- d) δ : 5.96 (d, 1 H, $J = 10$, olefinic), 6.33 (d, 1 H, $J = 17$, olefinic), 6.75 (dd, 1 H, $J = 10$ and 17, olefinic), 7.55 (m, 3 H, aromatic), 7.85 (m, 2 H, aromatic).

9. Earlier citations³ report bp $105\text{--}110^\circ\text{C}$ (1.5 mm) and $93\text{--}95^\circ\text{C}$ (0.2 mm).

10. This product has the following spectral properties: IR (neat) cm^{-1} : 3025, 1720, 1680, 1480, 1440, 1045, 750, and 690; ^1H NMR (chloroform- d) δ : 5.63-6.17 (m, 2 H, olefinic H), 6.44-6.87 (m, 1 H, olefinic H), 7.10-7.55 (m, 5 H, aromatic H).

3. Discussion

The procedure for oxidation of the sulfide to the sulfone is based on that reported earlier by Bordwell and Pitt.⁴ The synthetic utility of phenyl vinyl sulfone and sulfoxide derives not only from their ability to serve as excellent Michael acceptors toward such reagents as enolate anions and organometallics,⁵⁻¹² but also as moderately reactive dienophiles in Diels-Alder reactions.¹³⁻¹⁶ The resulting adducts, in turn, can be chemically modified so that these electron-deficient olefins serve as useful synthons for acetylene,¹³ ethylene,¹⁴ terminal olefins,¹⁵ vinylsilanes,¹⁷ and ketene¹⁸ in [4 + 2] cycloadditions. Phenyl vinyl sulfone undergoes ready cycloaddition to Danishefsky's diene in the first step of a protocol for the regiospecific γ -alkylation of 2-cyclohexenones.¹⁹ Furthermore, the ready lithiation of phenyl vinyl sulfones²⁰ and sulfoxides²¹ represents a convenient route to α -(phenylsulfonyl)- and α -(phenylsulfinyl)vinylolithium reagents.

The method described here for the preparation of phenyl vinyl sulfoxide is superior to that which involves reaction of ethyl phenyl sulfinate with vinylmagnesium bromide.¹³

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Phenyl vinyl sulfone: Sulfone, phenyl vinyl (8); Benzene, (ethenylsulfonyl)- (9); (5535-48-4)

Phenyl vinyl sulfoxide: Sulfoxide, phenyl vinyl (8); Benzene, (ethenylsulfinyl)- (9); (20451-53-0)

Benzenethiol (8, 9); (108-98-5)

1,2-Dibromoethane: Ethane, 1,2-dibromo- (8, 9); (106-93-4)

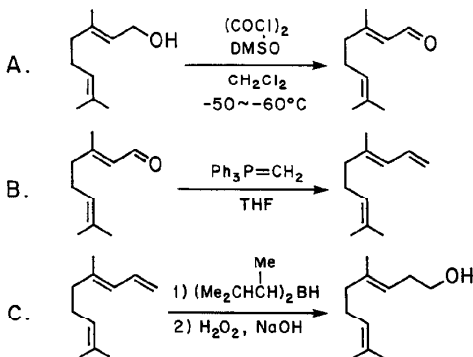
Phenyl vinyl sulfide: Sulfide, phenyl vinyl (8); Benzene, (ethenylthio)- (9); (1822-73-7)

m-Chloroperbenzoic acid: Peroxybenzoic acid, m-chloro- (8);

Benzenecarboperoxoic acid, 3-chloro- (9); (937-14-4)

SELECTIVE HYDROBORATION OF A 1,3,7-TRIENE: HOMOGERANLIOL

(3,7-Nonadien-1-ol, 4,8-dimethyl-, (E)-)



Submitted by Eric J. Leopold.¹

Checked by Shridhar Hegde and Robert M. Coates.

1. Procedure

A. *Geranial*. A 2-L, three-necked, round-bottomed flask is dried in an oven and equipped with a mechanical stirrer, thermometer, Claisen adapter, and two pressure-equalizing dropping funnels. The flask is charged with 500 mL of dichloromethane (Note 1) and 20 mL (29.2 g, 0.23 mol) of oxalyl chloride (Note 2). The solution is stirred and cooled at -50 to -60°C as 34 mL (37.5 g, 0.48 mol) of dimethyl sulfoxide (Note 3) in 100 mL of dichloromethane is added dropwise at a rapid rate. After 5 min 30.8 g (0.2 mol) of geraniol (Note 4) is added dropwise over 10 min maintaining the temperature at -50 to -60°C.

After another 15 min, 140 mL of triethylamine is added dropwise while keeping the temperature at or below -50°C . Stirring is continued for 5 min after which the mixture is allowed to warm to room temperature and 700 mL of water is added. The aqueous layer is separated and extracted with two 300-mL portions of dichloromethane. The organic layers are combined, washed with two 100-mL portions of saturated sodium chloride, and dried over anhydrous magnesium sulfate. The filtered solution is concentrated to 500 mL by rotary evaporation and washed successively with 1% hydrochloric acid until no longer basic. The dichloromethane solution is washed with water, 5% sodium carbonate, water, and saturated sodium chloride before drying over anhydrous magnesium sulfate. Rotary evaporation of the solvent gives ca. 30 g of crude product. Distillation in a Kugelrohr apparatus (Note 5) with an oven temperature of $80\text{--}85^{\circ}\text{C}$ (1 mm) affords 27.3–28.5 g (90–94%) of geranial, n_D^{24} 1.4870 (Note 6).

B. (*E*)-4,8-Dimethyl-1,3,7-nonatriene. A 1-L, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirring bar, and serum caps (Note 7) is charged with 50 g (0.12 mol) of methyltriphenylphosphonium iodide (Note 8) and 320 mL of tetrahydrofuran (Note 9) and is flushed with argon. The flask is cooled in an ice bath and the suspension is stirred under a positive pressure of argon, while about 0.2–0.6 mL of 2.05 M phenyllithium in 30:70 ether-cyclohexane (Notes 10 and 11) is added dropwise until the suspension develops a permanent yellow color (Note 12). Then 56 mL (0.115 mol) of 2.05 M phenyllithium is added dropwise over 10 min. The ice bath is removed, and the orange suspension containing excess phosphonium salt is stirred at room temperature for 30 min. The reaction mixture is stirred and cooled at 0 to 5°C , and 17.2 g (0.11 mol) of geranial in 50 mL of tetrahydrofuran is added dropwise over 10

min. The dropping funnel is rinsed with a small amount of tetrahydrofuran. The mixture is stirred at room temperature for 2 hr. The light orange mixture is hydrolyzed by adding 2 mL of methanol, and most of the solvent is removed on a rotary evaporator until a slurry results (Note 13). The slurry is diluted with 200 mL of petroleum ether (bp 60-68°C), and the supernatant solution is decanted and filtered through 150 g of Celite on a Büchner funnel. The solids remaining in the flask are heated with three 100-mL portions of hot petroleum ether and the supernatant solutions are also filtered through Celite. The filtrate is concentrated by rotary evaporation to a yellowish liquid which is filtered through 150 g of Florisil on a Büchner funnel, and the Florisil is washed with 300 mL of petroleum ether. Rotary evaporation of the eluate provides ca. 15 g of clear liquid which upon distillation in a Kugelrohr apparatus with an oven temperature of 60-70°C (2 mm) gives 13.1-13.5 g (77-80%) of the triene, n_D^{22} 1.4871 (Notes 14 and 15).

C. Homogeraniol. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to maintain a positive argon pressure within the apparatus (Note 7). The flask is charged with 102 mL (94.8 mmol) of 0.93 M diborane in tetrahydrofuran (Note 16), and the contents are cooled to -30°C. The diborane solution is stirred as 22.1 mL (0.21 mol) of 2-methyl-2-butene (Note 17) is added rapidly. Stirring is continued for 2 hr while maintaining the temperature at 0 to 2°C. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to keep a positive pressure of argon (Note 7) is charged with 13.0 g (86.7 mmol) of (E)-4,8-dimethyl-1,3,7-nonatriene and 35 mL of tetrahydrofuran (Note 9). The contents are stirred and cooled at 0°C as the solution of disiamylborane in the first flask

is transferred via cannula to the pressure-equalizing dropping funnel attached to the second flask. After approximately 20 mL of disiamylborane is transferred to the dropping funnel via cannula, the dropwise addition of the disiamylborane is started while the transfer continues. The remainder of the disiamylborane solution in the first flask is kept at 0°C. After the 1-hr addition is completed, stirring is continued for 1 hr at 0°C and overnight at room temperature (15 hr). Excess disiamylborane is destroyed by adding 2 mL of ethanol, the mixture is cooled to 0°C, and 33 mL of 3 M sodium hydroxide is added rapidly. Stirring and cooling at -10°C are continued as 33 mL of chilled 30% hydrogen peroxide is slowly added (Note 18). The reaction mixture is stirred at room temperature for 3 hr, the layers are separated, and the aqueous layer is extracted with two 75-mL portions of ether (Note 19). The combined organic layers are washed with two 25-mL portions of saturated sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent gives ca. 21 g of crude product which is purified by chromatography on 400 g of silica gel packed in a 7.5-cm by 20-cm column. The column is eluted with dichloromethane and 100-mL fractions are collected, the first two of which are discarded. Elution is continued by collecting the 100-mL fractions in a weighed flask and evaporating the solvent under reduced pressure until a constant weight of product is obtained (nine 100-mL fractions). Distillation of the residue in a Kugelrohr apparatus with an oven temperature of 150°C (0.02 mm) gives 12.6-13.2 g (88-91%) of homogeraniol, n_D^{21} 1.4740 (Note 20).

2. Notes

1. Dichloromethane was distilled from calcium hydride and stored over Linde Molecular Sieves Type 4A.

2. Oxalyl chloride was distilled immediately before use.
3. Dimethyl sulfoxide was distilled from calcium hydride and stored over Linde Molecular Sieves Type 3A.
4. Geraniol was obtained from Aldrich Chemical Company, Inc. (Gold Label) and used without purification.
5. Kugelrohr ovens are available from Rinco Instrument Co., Inc., 5035 Prairie St., P.O. Box 167, Greenville, IL 62246.
6. Thin-layer chromatographic analysis of the product by the submitter on silica gel with 20% ethyl acetate in hexane as developing solvent showed one spot, R_f 0.5. Gas chromatographic analysis showed the presence of 1.5% of the cis isomer by coinjection with 40:60 cis-trans citral mixture available from Aldrich Chemical Company, Inc. The ^1H NMR spectral data for the product are as follows δ : 1.61 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.19-2.23 (m, 4 H, CH_2CH_2), 5.06 (br s, 1 H, vinyl H at C-6), 5.88 (d, 1 H, $J = 8$, vinyl H at C-2), 9.99 (d, $J = 8$, CHO).
7. The glassware was dried in an oven at 150°C , assembled while still hot, and alternately evacuated and flushed with argon.
8. Methyltriphenylphosphonium iodide was prepared by the following procedure. Triphenylphosphine was recrystallized from ethanol and dried over phosphorus pentoxide under reduced pressure for 12 hr. A solution of 39 g (0.15 mol) of triphenylphosphine and 10.0 mL (22.8 g, 0.16 mol) of iodomethane in 105 mL of benzene was allowed to stir at room temperature for 12 hr. The precipitate was filtered, washed with benzene, and dried over phosphorus pentoxide under reduced pressure for 12 hr. The yield was 57 g (94%), mp 189°C (lit. 2 mp, 182°C). The reagent is also available from Aldrich Chemical Company, Inc.
9. Tetrahydrofuran was distilled from sodium-benzophenone ketyl.

10. The phenyllithium solution was purchased from Aldrich Chemical Company, Inc. The checkers used 64 mL (0.115 mol) of 1.8 M phenyllithium in 75:25 benzene-ether which was purchased from Alpha Products, Morton/Thiokol Inc.

11. The submitter states that the slight excesses of phenyllithium (5%) and methyltriphenylphosphonium iodide (10%) specified ensure complete conversion of the aldehyde and simplify the purification of the product since the excess phosphonium salt is readily removed during filtration through Florosil.

12. The addition of 0.2-0.6 mL of the phenyllithium solution presumably destroys small amounts of moisture or other impurities.

13. The submitter cautions against evaporating all of the solvent; the triphenylphosphine oxide will tenaciously occlude the product, and the yield will be reduced.

14. A gas chromatographic analysis of the product by the submitter on a 15-M capillary column coated with silicone oil SE-54 at 70°C showed one peak (98%).

15. An index of refraction of 1.4826 at 20°C is reported³ for the product. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 3080, 1645, 1600, 1345, 990, 900; ^1H NMR (CDCl_3) δ : 1.61 (3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3 at C-4), 1.95-2.12 (broad, 4 H, CH_2CH_2), 4.80-5.15 (broad (3 H, vinyl H), 5.85 (d, 1 H, $J = 10$, vinyl H at C-3), 6.55 (3 d, $J = 10, 10, 17$, vinyl H at C-2).

16. The diborane solution was obtained from Aldrich Chemical Company, Inc. It was titrated⁴ before use although the submitter states that this is not necessary. The solution was transferred from the stock solution to the reaction flask via a cannula. The checkers first transferred the diborane

solution via a cannula into a graduated cylinder that was capped with a rubber septum and purged with nitrogen. The specified volume was then transferred into the reaction vessel.

17. 2-Methyl-2-butene was obtained from Aldrich Chemical Company, Inc. and was distilled from calcium hydride.

18. The oxidation of organoboranes is exothermic, and efficient cooling and slow addition are necessary to keep the temperature near 0°C.⁵

19. The checkers observed the separation of a heavy, white precipitate presumed to be a borate salt during the addition of hydrogen peroxide. After the three-phase mixture had been stirred at room temperature for 3 hr, the liquid layers were decanted into a separatory funnel. The solid remaining in the flask was washed with two 75-mL portions of ether and these washings were used to extract the aqueous layer.

20. Indices of refraction of 1.4722 at 22°C and 1.4718 at 26°C are reported for homogeraniol.^{6,7} The spectral properties of the product are as follows: IR (neat) cm^{-1} : 3330, 2960 (sh), 2920, 1448, 1435 (sh, m), 1374 (m), 1108 (w), 1045 (s), 875 (w); ¹H NMR (CDCl_3) δ : 1.60 (s, 3 H, CH_3 at C-4), 1.64 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3 at C-4), 1.95-2.15 (s, 4 H, CH_2CH_2), 2.30 (m, 2 H, $\text{CH}_2\text{CH}_2\text{OH}$), 3.60 (t, 2 H, $J = 7$, CH_2OH), 4.95-5.25 (m, 2 H, vinyl H).

3. Discussion

Homogeraniol is an important intermediate in syntheses of squalene,⁶ aplycistatin,⁸ dendrolacin,⁹ and juvenile hormone analogues.¹⁰ The present procedure affords an efficient, stereoselective method for preparing (E)-homogeraniol, contaminated by at most 1-2% of the Z isomer.

In Part A geraniol is oxidized to geranial (citral) by Swern's modification of the Moffat oxidation.¹¹ The stereoisomeric purity of the product is at least 98%. This procedure is readily conducted on a large-scale and requires only 4 hours' time including distillation of oxalyl chloride. The oxidation of geraniol to pure (E)-geranial may also be accomplished by Collin's oxidation with chromium trioxide-dipyridine complex,¹² or by use of activated manganese dioxide.¹³ However, these methods require large amounts of reagents and solvents for 0.2-mol scale preparations.

The Wittig methylenation of geranial to (E)-4,8-dimethyl-1,3,7-nonatriene is best carried out with phenyllithium in tetrahydrofuran as described in Part B. The use of butyllithium in tetrahydrofuran or ether-hexane³ affords the triene in only 50-60% yield. When the ylide was generated with sodium hydride or potassium tert-butoxide in dimethyl sulfoxide by the submitter, the Wittig reaction gave triene containing 10-20% of the Z isomer. Part C illustrates the selective hydroboration of a diene with disiamylborane.¹⁴ The reaction is best carried out by adding preformed disiamylborane to the triene. Lower yields of homogeraniol were obtained by the submitter when the triene was added to the borane reagent.

Homogeraniol has been prepared by reduction of homogeranic acid with lithium aluminum hydride,⁶ by cyclopropylcarbinol rearrangement to homogeranyl bromide and subsequent displacement of the bromide,¹⁵ by zirconium-catalyzed cis addition of trimethylaluminum to an acetylene precursor followed by reaction with ethylene oxide,⁷ and by hydroxymethylation of geranyl chloride with diisopropoxymethylsilylmethyl Grignard reagent.¹⁶ Homogeranic acid has been prepared by base-catalyzed hydrolysis of the nitrile,^{6,9,17} by copper-catalyzed S_N2 -type alkylation of β -isopropenyl- β -propiolactone with dimethylallyl Grignard reagent,¹⁸ by alkylation of methoxy(phenylthio)-

methyllithium with geranyl chloride and subsequent chromic acid oxidation,¹⁹ and by carboxylation of geranyl phenyl sulfone followed by reductive desulfonation.²⁰ Although homogaranic acid prepared by nitrile hydrolysis and by β -isopropenyl- β -propiolactone alkylation¹⁸ is a 70:30 mixture of E and Z isomers,^{9,21a} the E form may be isolated by crystallization at -10°C ⁶ or by preparative gas chromatography of their tert-butyl esters.^{21b} Homogeraniol prepared by acid-catalyzed cyclopropylcarbiny to homoallyl rearrangement¹⁵ is also a mixture of E and Z isomers.²²

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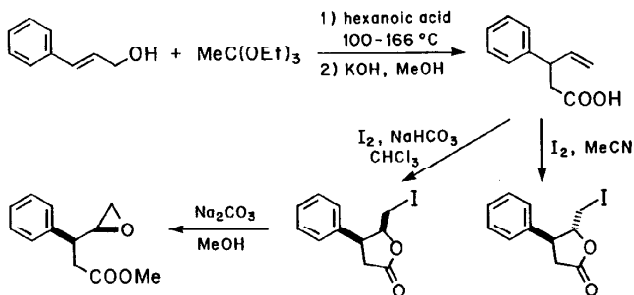
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- Homogeraniol: 3,7-Nonadien-1-ol, 4,8-dimethyl-, (E)- (9); (459-88-1)
- Geranial: 2,6-Octadienal, 3,7-dimethyl- (8,9); (5392-40-5)
- Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)
- Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)
- Geraniol: 2,6-Octadien-1-ol, 3,7-dimethyl-, (E)- (8,9); (106-24-1)
- (E)- 4,8-Dimethyl-1,3,7-nonatriene: 1,3,7-Nonatriene, 4,8-dimethyl-, (E)- (8,9); (19945-61-0)
- Methyltriphenylphosphonium iodide: Phosphorane, iodomethyltriphenyl- (9); (20667-19-0)
- Phenyllithium: Lithium, phenyl- (8,9); (591-51-5)
- Diborane-tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1:1) (8,9); (14044-65-6)
- 2-Methyl-2-butene: 2-Butene, 2-methyl- (8,9); (513-35-9)
- Disiamylborane: Borane, bis(1,2-dimethylpropyl)- (8,9); (1069-54-1)

STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC ACIDS: THE TRANS
AND CIS ISOMERS OF 4,5-DIHYDRO-5-IODOMETHYL-4-PHENYL-2(3H)-FURANONE



Submitted by F. Bermejo González and Paul A. Bartlett.¹

Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. 3-Phenyl-4-pentenoic acid. A mixture of 33.7 g (0.25 mol) of cinnamyl alcohol (Note 1), 46.1 mL (0.25 mol) of triethyl orthoacetate (Note 1), and 0.19 mL (1.5 mmol) of hexanoic acid (Note 2) is placed in a 250-mL, round-bottomed flask equipped with a thermometer, Claisen head, and condenser. The solution is heated in an oil bath with distillation of ethanol. After 3 hr, distillation of ethanol slows and another 0.1-mL portion of hexanoic acid is added. Additional portions (0.1 mL) of the catalyst are added again at 3.5 and 4.5 hr. After 6 hr, a total of 27 mL of ethanol, out of a theoretical 29.2 mL, has been collected, and GC analysis (Note 3)

indicates that no cinnamyl alcohol remains. Over this 6-hr period the internal temperature rises from 100°C to 166°C.

The solution is allowed to cool, and 19.7 g (0.35 mol) of potassium hydroxide in 25 mL of water and 75 mL of methanol is added. The mixture is heated under reflux for 1 hr under nitrogen. After the alkaline solution is allowed to cool to room temperature, it is washed with ether and acidified with concd HCl. The acidic solution is extracted with three 50-mL portions of ether, and the organic layer is dried over MgSO_4 , filtered, and concentrated under reduced pressure. The yield of crude 3-phenyl-4-pentenoic acid is 38-39 g (86-88%). This material is essentially pure by NMR analysis and can be used directly as starting material for the following iodolactonization reactions. The acid can be further purified by crystallization from hexane (86% recovery in two crops) to give product melting at 44-46°C.

B. Thermodynamically-controlled formation of the trans (4RS,5SR) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone. In a 500-mL, round-bottomed flask equipped with a mechanical stirrer (Note 4) and immersed in an ice bath is placed a solution of 10 g (0.057 mol) of 3-phenyl-4-pentenoic acid in 200 mL of acetonitrile (Note 5). Solid iodine (44.5 g, 0.18 mol) (Note 6) is added, and the mixture is protected from light and stirred at 0°C under nitrogen for 24 hr. The mixture is partitioned between 100 mL of ether and 100 mL of saturated aq NaHCO_3 . The organic layer is washed with 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ until colorless, and with water and brine. It is then dried over MgSO_4 , the solvent is removed at reduced pressure, and the crude trans iodolactone is obtained as a thick oil; weight 14.5-15.6 g (85-91%). NMR analysis indicates that the trans to cis ratio is at least 95:5 (Note 7).

C. Kinetically-controlled formation of the cis (4RS,5RS) isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone. A mixture of 10 g (0.057 mol)

of 3-phenyl-4-pentenoic acid, 9.1 g (0.11 mol) of NaHCO_3 and 200 mL of water is placed in a 1000-mL round-bottomed flask equipped with a mechanical stirrer (Note 4), and stirred until a homogeneous solution is obtained. Chloroform (200 mL) is added, the mixture is cooled in an ice bath, and 28.4 g (0.112 mol) (Note 8) of iodine is added. The mixture is stirred at 0°C for 6 hr, the layers are separated, and the organic phase is washed with 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ until colorless, and with water and brine. The organic layer is dried over MgSO_4 , the solvent is removed under reduced pressure, and the crude cis iodolactone is obtained as a semisolid: weight 15.5-16.3 g (91-95%), mp 75-90°C (Note 9). Direct recrystallization of this material from diisopropyl ether (Note 10) affords 9.0-9.5 g (52-55%) of material, mp 103-104°C, with a cis/trans ratio of 15-16:1. Further recrystallization from diisopropyl ether gives (in two crops) 8.3-8.9 g (48-52%) of product, mp 104-105°C, with a purity of >98%. Additional product can be obtained from the mother liquors.

2. Notes

1. The reagents employed were obtained from Aldrich Chemical Company and used as received.

2. Propionic acid may also be used as catalyst; however, its boiling point (141°C) is below that of the reaction temperature at the end of the reaction. The use of o-nitrophenol as catalyst resulted in a lower yield in this case.

3. GC analysis was performed on a Varian model 940 gas chromatograph equipped with a 6' x 1/8" column of 5% OV-101 on Gas-Chrom Q at a column temperature of 155°C.

4. A magnetic stirrer is not recommended because the mixture becomes very thick.
5. Mallinckrodt Inc. analytical reagent grade acetonitrile was used.
6. Two equivalents of iodine are required by the stoichiometry of the reaction, because of formation of HI_3 . In our experience, however, the reaction does not proceed to completion without additional reagent.
7. The crude trans isomer obtained in this way is of suitable purity for conversion to the epoxy ester, as described below (see Discussion). It may be further purified by column chromatography; however, attempted vacuum distillation leads to considerable decomposition.
8. Two equivalents of iodine are required because of formation of NaI_3 .
9. NMR analysis of the crude iodolactone indicates that the cis:trans ratio is about 3.4:1.
10. The recrystallization is performed using ca. 15 mL of diisopropyl ether per gram of crude product. Dichloromethane, 1-2%, is also added to the hot mixture to effect complete solution before cooling.

3. Discussion

Iodolactonization has become a useful reaction for the sterecontrolled introduction of chiral centers in both cyclic² and acyclic³⁻⁹ systems. Depending upon the reaction conditions, the cyclization can be carried out under either kinetic or thermodynamic control.^{3,10} The contrast between the stereochemical course of the two procedures is not always as dramatic as with 3-phenyl-4-pentenoic acid, as illustrated by the examples in Table I.¹¹

Conversion of iodolactones into the corresponding epoxy esters is often one of the major steps in their utilization for the purposes of stereo-control.^{3 7,12} Methanolysis of the cis isomer of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone to methyl (3RS,4RS)-4,5-epoxy-3-phenylpentanoate is a representative procedure for this transformation.

A mixture of 5.0 g (16.6 mmol) of (4RS,5RS)-4,5-dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone (cis isomer), 75 mL of methanol, and 1.8 g (17.0 mmol) of finely powdered, anhydrous Na_2CO_3 is placed in a 250-mL, round-bottomed flask equipped with a mechanical stirrer, and heated under nitrogen at reflux for 8 hr. The resulting solution is concentrated under reduced pressure to a volume of 50 mL and partitioned between 100 mL of water and 100 mL of ether. The organic layer is washed with water and brine, dried over MgSO_4 , and evaporated to give 3.1 g (91%) of crude product. This material, which shows only minor impurities by NMR spectroscopy, can be further purified by chromatography (silica gel/1:1 ether:hexane) (98% recovery) and bulb-to-bulb distillation (78°C/0.045 mm) (82% recovery).

TABLE I
IODOLACTONIZATION OF OLEFINIC ACIDS

Substrate	Trans:Cis Ratio [Yield (%)]	
	"Thermodynamic Control"	"Kinetic Control"
3-Methyl-4-pentenoic acid	10:1 (84)	1:3 (82)
4-Methyl-5-hexenoic acid	10:1 (77)	1:2.3 (83)
3-Methyl-5-hexenoic acid	1:6 (81)	1:3 (97)
2-Methyl-5-hexenoic acid	1.1:1 (68)	1.9:1 (78)
(2RS,4SR)-2,4-Dimethyl-5-hexenoic acid	20:1 (89)	3.5:1

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

trans-4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone: 2(3H)-Furanone, dihydro-5-(iodomethyl)-4-phenyl, trans- (10); (67279-69-0)

cis-4,5-Dihydro-5-iodomethyl-4-phenyl-2(3H)-furanone: 2(3H)-Furanone, dihydro-5-(iodomethyl)-4-phenyl-, cis- (10); (67279-70-3)

Cinnamyl alcohol (8); 2-Propen-1-ol, 3-phenyl- (9); (104-54-1)

Triethyl orthoacetate: Orthoacetic acid, triethyl ester (8):

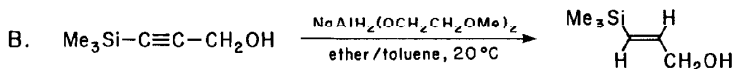
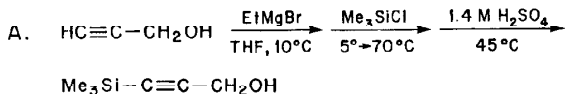
Ethane, 1,1,1-triethoxy- (9); (78-39-7)

Hexanoic acid (8,9); (142-62-1)

STEREOSPECIFIC REDUCTION OF PROPARGYL ALCOHOLS:

(E)-3-TRIMETHYLSILYL-2-PROPEN-1-OL

(2-Propen-1-ol, 3-(trimethylsilyl)-, (E)-)



Submitted by Todd K. Jones and Scott E. Denmark.¹

Checked by Steven M. Viti and K. Barry Sharpless.

1. Procedure

A. *3-Trimethylsilyl-2-propyn-1-ol*. A 3-L, three-necked, round-bottomed flask (equipped with a mechanical stirrer and a thermometer) is fitted with a Claisen adapter on which is mounted a 250-mL pressure equalizing addition funnel and a reflux condenser (Note 1). The apparatus is flushed with nitrogen and then charged with 48.7 g (2.0 mol) of magnesium turnings and 1 L of dry tetrahydrofuran (Note 2). To the stirred suspension is added dropwise 149.5 mL (218.3 g, 2.0 mol) of bromoethane over 3 hr maintaining the temperature at 50°C or less. After complete addition, the gray-green solution is heated at 50°C for 1 hr and then cooled to 5°C on ice. A solution of 41.6 mL (40.5 g, 0.72 mol) of propargyl alcohol (Note 3) in 42 mL of tetrahydrofuran is cautiously added dropwise to the gray suspension over 2.25 hr

maintaining the temperature at 10°C or less (Note 4). The addition funnel is rinsed with 25 mL of tetrahydrofuran and the gray-green suspension is stirred overnight. The resulting solution is cooled to 5°C on ice and the addition funnel is charged with 254 mL (217 g, 2.0 mol) of chlorotrimethylsilane (Note 5). This is added dropwise to the stirred solution over 1 hr maintaining the temperature at 25°C or less by external cooling with ice. After complete addition, the mixture is heated to reflux for 2 hr with a heating mantle (Note 6). The suspension is cooled to 20°C on ice and then 800 mL of 1.4 M aqueous sulfuric acid is cautiously added over 0.75 hr so that the temperature remains below 45°C. The resulting solution is stirred for 5 min and then 600 mL of ether is added. Both phases are transferred to a 4-L separatory funnel and the layers are separated. The aqueous phase is extracted twice with 400-mL portions of ether and all ether layers are individually washed in series with two 1-L portions of water and once with 800 mL of saturated sodium chloride solution. The combined organic extracts are dried over magnesium sulfate and concentrated by rotary evaporation. The yellow-brown residue is purified by short path distillation to afford 82-86 g (91-94% yield) of 3-trimethylsilyl-2-propyn-1-ol as a clear, colorless liquid (Note 7), bp 76°C (20 mm) (Note 8).

B. (E)-3-Trimethylsilyl-2-propen-1-ol. A three-necked, 2-L, round-bottomed flask fitted with a thermometer, nitrogen inlet, 250-mL pressure-equalizing addition funnel, and a magnetic stirring bar is charged with 147 mL of a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, Note 9) and 200 mL of anhydrous ether (Note 10). The SMEAH solution is cooled to 3°C on ice and then treated dropwise from the addition funnel with a solution of 40 g (0.31 mol) of 3-trimethylsilyl-2-propyn-1-ol in 180 mL of ether over 1.25 hr maintaining the temperature at 5°C or less. Ten minutes after complete addition the ice bath is removed and the reaction is complete

within 1 hr (Note 11). The mixture is cooled to 0°C and then quenched by the addition of 1 L of 3.6 M aqueous sulfuric acid (Note 12). The layers are separated in a separatory funnel and the aqueous phase is extracted twice with 200-mL portions of ether. All ether layers are individually washed in series with two 200-mL portions of water and once with 200 mL of saturated sodium chloride. The combined organic extracts are dried over magnesium sulfate and concentrated by rotary evaporation. Distillation of the yellow residue with a capillary bleed affords 21.7-29.0 g (68-71%) of (E)-3-trimethylsilyl-2-propen-1-ol (Note 13) as a clear, colorless liquid, bp 73-75°C (20 mm) (Note 14).

2. Notes

1. It is not necessary to flame or oven dry this apparatus but a nitrogen inlet on the reflux condenser is desirable. The size of the stirring paddle is critical because of the viscous nature of the solution during this protection step. A paddle at least 11 cm in length is recommended to ensure complete mixing.

2. Magnesium turnings and bromoethane are Mallinckrodt AR grade and are used without purification. Tetrahydrofuran is Aldrich Gold Label and is distilled from sodium benzophenone ketyl prior to use.

3. Propargyl alcohol is obtained from Aldrich Chemical Company, Inc., and is distilled from potassium carbonate.

4. Evolution of ethane can conveniently be monitored with a Nujol bubbler in the nitrogen line by turning off the nitrogen flow.

5. Chlorotrimethylsilane is purchased from Silar and used as received.

6. The progress of the reaction can be monitored by gas chromatography. Column: 5% Carbowax 12 M on acid-washed Chromosorb W, 6 ft x 1/8 in; temperature program: 70°C (2 min), 20°C/min, 200°C (5 min). Retention times: propargyl alcohol, 2.4 min; 3-trimethyl-2-propyn-1-ol, 4.8 min.

7. *CAUTION* - The distillation pot may ignite if it is exposed to air before it is allowed to cool. The product thus obtained is 94-98% pure by GC analysis and is of suitable purity for reduction. Further purification can be effected by distillation through a 6 in Vigreux column.

8. The product has the following spectral characteristics: ^1H NMR (90 MHz, CDCl_3) δ : 4.28 (s, 2 H, 2 H-C(1)); 1.65 (s, 1 H, OH); 0.27 (s, 9 H, $(\text{CH}_3)_3\text{Si}$).

9. Sodium bis(2-methoxyethoxy)aluminum hydride is obtained as a 70% solution in toluene from Aldrich Chemical Company, Inc. (Red- Al^{R}). Iodometric titration gives a 3.6 M concentration.

10. Anhydrous ether is obtained from Mallinckrodt Inc. (AR grade) and used without purification.

11. The reaction can be monitored by gas chromatography (Note 6), temperature program: 70°C (2 min), 20°C/min, 150°C (2 min). Retention times: (E)-3-trimethylsilyl-2-propen-1-ol, 4.2 min; 3-trimethylsilyl-2-propyn-1-ol, 6.1 min.

12. A vigorous evolution of hydrogen accompanies the addition of the first milliliters of sulfuric acid. The reaction mixture becomes gelatinous and unstirrable, but clarifies upon further addition of acid.

13. The product is 100% E geometry by GC analysis.

14. The product has the following spectral characteristics: ^1H NMR (90 MHz, CDCl_3) δ : 6.23 (d of t, 1 H, $J = 18$ and 4, H-C(2)); 5.93 (d, 1 H, $J = 18$, H-C(3)); 4.22 (d of d, 2 H, $J = 6$ and 4, 2 H-C(1)); 1.5 (t, 1 H, $J = 6$, OH); 0.23 (s, 9 H, $(\text{CH}_3)_3\text{Si}$).

3. Discussion

The silylation of propargyl alcohol dianion^{2a} described here is a further modification of the procedure recently reported.^{2b} By replacing ether with tetrahydrofuran the reaction mixture is more manageable and the silyl ether can be hydrolyzed in situ obviating an unnecessary workup and distillation. The yield correspondingly improves up to 91-94%. Silylation of the dilithium salt in ether is reported³ to proceed in 86% yield.

Reduction of 3-trimethylsilyl-2-propyn-1-ol exemplifies the problem of stereoselectivity in hydride reduction of acetylenic alcohols to E-allyl alcohols.⁴ Early reports⁵ that lithium aluminum hydride stereoselectively reduced acetylenic alcohols gave way to closer scrutiny which revealed a striking solvent dependence of the stereochemistry.⁶ Specifically, the percentage of trans reduction is seen to increase with increasing Lewis basicity of solvent. Similarly, the addition of less Lewis acidic cations to the reducing mixture leads to improved trans/cis ratios.⁷ Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH)⁸ makes use of these phenomena simultaneously (even in ether-toluene mixtures) and leads to completely stereospecific trans reduction where lithium aluminum hydride in various solvents or with sodium methoxide is less selective.^{2b,9,10a,b} The use of SMEAH to reduce stereospecifically other acetylenic alcohols has been reported.¹¹

(F)-3-Trimethylsilyl-2-propen-1-ol is a versatile intermediate used to introduce organosilicon functional groups into organic molecules.^{9,12} The corresponding aldehyde has found use in the preparation of β -silyl divinyl ketones¹³ and as a precursor for 1-trimethylsilyl-substituted dienes.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(E)-3-Trimethylsilyl-2-propen-1-ol: 2-Propen-1-ol, 3-(trimethylsilyl)-, (E)- (9); (59376-64-6)

3-Trimethylsilyl-2-propyn-1-ol: 2-Propyn-1-ol, 3-(trimethylsilyl)- (9); (5272-36-3)

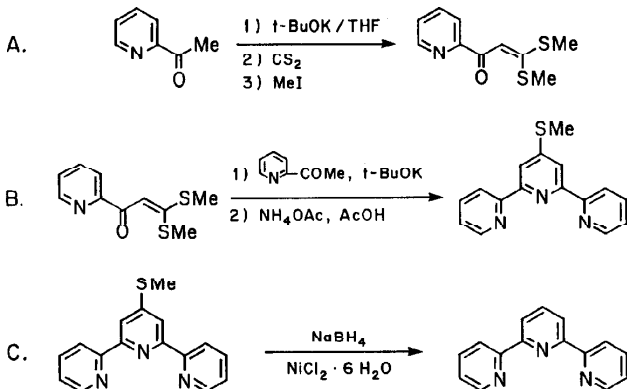
Bromoethane: Ethane, bromo- (8,9); (74-96-4)

Propargyl alcohol: 2-Propyn-1-ol (8,9); (107-19-7)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Sodium bis(2-methoxyethoxy)aluminum hydride: Aluminate (1-), dihydrobis(2-methoxyethanolato)-, sodium (8); Aluminate (1-), dihydrobis(2-methoxyethanolato-0,0')-, sodium (9); (22722-98-1)

2,2':6',2''-TERPYRIDINE



Submitted by Kevin T. Potts, Philip Ralli, George Theodoridis,
and Paul Winslow.¹

Checked by B. L. Chenard and Bruce E. Smart.

1. Procedure

A. *3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one*. A 3-L, three-necked flask is equipped with an efficient mechanical stirrer, pressure equalizing dropping funnel with needle valve, and a reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler. The system is flushed with nitrogen, and while the system is maintained under a static pressure of nitrogen, the flask is charged with 1000 mL of dry

tetrahydrofuran (Note 1) and 96.5 g (0.86 mol) of potassium tert-butoxide (Note 2). Freshly distilled 2-acetylpyridine (50.0 g, 0.41 mol) (Note 3) is then added dropwise over a period of 5-10 min (Note 4). To the resulting reaction mixture 32.7 g (0.43 mol) of carbon disulfide is added over a period of 30-35 min. After the addition is completed, 122.1 g (0.86 mol) of methyl iodide is added over 1 hr to the viscous, heterogeneous orange reaction mixture. After the tan reaction mixture is stirred for 12 hr at room temperature, it is poured into 2 L of iced water and allowed to stand for 4 hr. The solid that precipitates is collected by filtration and air dried to give 56 g (61%) of yellow crystals, mp 106-107°C. The filtrate is diluted with water to a total volume of 4 L, and chilled to afford an additional 16.5 g (18%) of product, mp 104-107°C (Note 5).

B. *4'-(Methylthio)-2,2':6',2''-terpyridine*. A 1-L, three-necked round-bottomed flask fitted with a mechanical stirrer and a gas inlet tube is flushed with nitrogen and charged with 500 mL of anhydrous tetrahydrofuran and 22.4 g (0.20 mol) of potassium tert-butoxide. Freshly distilled 2-acetylpyridine (12.1 g, 0.10 mol) (Note 3) is added, the solution is stirred for 10 min, and 22.5 g (0.1 mol) of 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one is then added. The mixture is stirred for 12 hr at room temperature, during which time it turns bright red and a red solid precipitates (Note 6). The mixture is next treated with 77 g (1.0 mol) of ammonium acetate and 250 mL of glacial acetic acid. A distillation head fitted with a thermometer is attached to the flask and the tetrahydrofuran is removed by distillation over a 2-hr period. The residual brown solution is chilled to 15°C, treated with 400 g of ice, and allowed to stand for 3 hr. Water (400 mL) is added, the mixture is chilled to 15°C, and the gray material that precipitates is collected by filtration, washed with iced water (3 x 200 mL), and air dried.

The crude product is taken up in 250 mL of boiling ethanol and filtered. The filtercake is rinsed with 50 mL of hot ethanol, and the hot filtrates are combined, diluted with 150 mL of water, concentrated to a volume of 400 mL, and allowed to cool to room temperature. After the mixture is thoroughly chilled in an ice bath, the precipitate is collected by filtration, washed with 50% aqueous ethanol, and dried under reduced pressure (23°C, 0.1 mm) to give 20.6-21.4 g (74-77%) of 4'-(methylthio)-2,2':6',2''-terpyridine as gray needles, mp 118-119°C (Note 7). This material is sufficiently pure for use in the following step.

C. *2,2':6',2''-Terpyridine.* A 1-L, four-necked flask equipped with a mechanical stirrer, pressure equalizing dropping funnel, thermometer, and a condenser fitted with a nitrogen gas inlet tube is flushed with nitrogen and charged with 300 mL of ethanol, 5.0 g (0.018 mol) of 4'-(methylthio)-2,2':6',2''-terpyridine, and 42.8 g (0.180 mol) of finely ground nickel chloride hexahydrate (Note 8). The resultant green heterogeneous mixture is chilled in an ice bath while the system is maintained under a static pressure of nitrogen. To this chilled (0-5°C) mixture, a solution of 20.4 g (0.54 mol) of sodium borohydride in 128 mL of 40% aqueous sodium hydroxide is added dropwise over 4 hr (Note 9). After the addition is completed and the evolution of hydrogen subsides, the dark reaction mixture is refluxed for 12 hr. The hot mixture is then filtered through a Celite pad, and the pad is washed with hot ethanol (3 x 100 mL). The filtrates are combined and evaporated to dryness under reduced pressure to yield a gray solid residue (Note 10). This solid is suspended in 300-400 mL of water and chilled in an ice bath for 4 hr. The cold suspension is filtered and the gray solid is air-dried. The crude product is taken up in 100 mL of boiling hexane and filtered. The filtrate is

concentrated to 50 mL, chilled in an ice bath, and filtered to give 2.48-2.53 g (59-60%) of 2,2':6',2''-terpyridine as cream colored prisms, mp 84-86°C [lit.² mp 85-86°C] (Notes 11, 12). The mother liquor is concentrated to 10 mL to give a second crop of 0.37-0.40 g (8.8-9.5%), mp 81-84°C.

2. Notes

1. The checkers used tetrahydrofuran which was distilled from lithium aluminum hydride (Caution: see *Org. Synth., Collect. Vol. V 1973*, 976) and stored with a chip of sodium metal. Distillation from sodium/benzophenone is preferable.

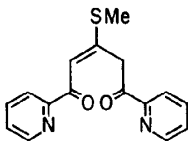
2. Potassium tert-butoxide was obtained from the Aldrich Chemical Company, Inc.

3. The checkers obtained 2-acetylpyridine from the Aldrich Chemical Company, Inc. The submitters thank Reilly Tar & Chemical Corp. for a generous gift of 2-acetylpyridine used in their work.

4. A light yellow solid precipitates during this addition.

5. The product is pure by ¹NMR (CDCl₃) δ: 2.55 (s, 3 H), 2.65 (s, 3 H), 7.40 (d of d of d, 1 H, J = 1.5, 5.6, 7.5), 7.65 (s, 1 H), 7.85 (d of t, 1 H, J = 7.5, 2.0), 8.20 (d of t, 1 H, J = 7.5, 1.5), 8.65 (d of m, 1 H, J = 7.5); IR (KBr) cm⁻¹: 1484, 1471. Analytically pure material, mp 108-109°C, may be obtained by recrystallization from ethanol.

6. This solid is the potassium salt of the enedione intermediate:



7. The checkers also obtained material with mp 116-118°C. The submitters report product of unspecified purity with mp 120-122°C. The material obtained by the checkers shows the following ^1H NMR (CDCl_3) δ : 2.0 (s, impurity), 2.67 (s, 3 H), 7.30 (d of d of d, 2 H, $J = 1.8, 5.6, 8.0$), 7.80 (d of t, 2 H, $J = 1.8, 8.0$), 8.35 (s, 2 H), 8.4-8.78 (m, 4 H). Mass spectrum m/e calculated: 279.0830. Found: 279.0815. IR (KBr) cm^{-1} : 1558, 1390. The combustion analyses for the products obtained by the checkers were within accepted limits for H, but off about 2% for C, and 0.6-0.8% for N.

8. Nickel chloride hexahydrate was obtained from the Fisher Scientific Company.

9. This reaction, which generates nickel boride,³ is exothermic and evolves hydrogen. Frothing is prevented by keeping the reaction mixture at 0-5°C during addition of the sodium borohydride.

10. The submitters report obtaining tan material.

11. This material is analytically pure. Anal. Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_3$: C, 77.23; H, 4.75; N, 18.01. Found C: 76.82; H, 4.69; N, 18.17. The product shows ^1H NMR (CDCl_3) δ : 7.33 (d of d of d, 2 H, $J = 1.5, 5.0, 8.0$), 7.86 (d of t, 2 H, $J = 2.0, 8.0$), 7.96 (t, 1 H, $J = 8.0$ H), 8.45 (d, 2 H, $J = 8.0$), 8.62 (d, 2 H, $J = 8.0$), 8.71 (d of m, 2 H).

12. The submitters report that 4'-(methylthio)-2,2':6',2''-terpyridine also can be conveniently reduced to 2',2'':6',2''-terpyridine with Raney nickel in ethanol. The checkers found, however, that this procedure invariably gave product contaminated with 4'-ethoxy-2,2':6',2''-terpyridine. Raney nickel which was exhaustively washed with water to remove base still gave 15% of this byproduct.

3. Discussion

The procedure described here is by far the most efficient synthesis of terpyridine.⁴ Previous preparations include the dehydrogenation of pyridine with ferric chloride,² the Ullman reaction of 2-bromopyridine and 2,6-dibromopyridine,⁵ the action of copper on 2-bromopyridine and 6-bromo-2,2'-dipyridyl,⁵ the reaction of iodine or ferric chloride with 2,2'-bipyridyl,⁵ and the reaction of 2,2'-bipyridyl with 2-lithiopyridine (40% yield).⁶

Terpyridine is a very effective chelating agent.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

Terpyridine: 2,2':6',2''-Terpyridine (8,9); (1148-79-4)

3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one: 2-Propen-1-one,

3,3-bis(methylthio)-1-(2-pyridinyl)- (9); (78570-34-0)

Potassium tert-butoxide: tert-Butyl alcohol, potassium salt (8); 2-Propanol,

2-methyl-, potassium salt (9); (865-47-4)

2-Acetylpyridine: Ethanone, 1-(pyridinyl)- (9); (30440-88-1)

Carbon disulfide (8,9); (75-15-0)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

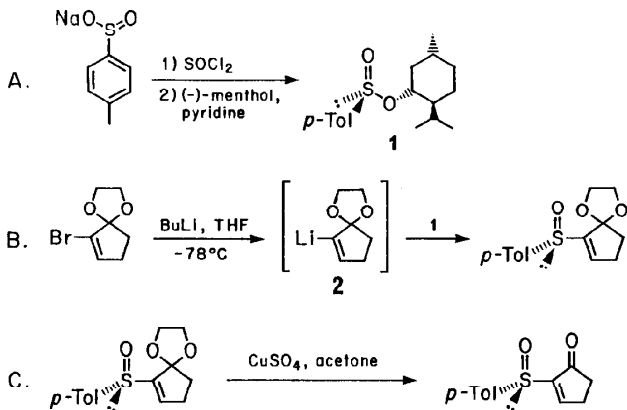
4'-(Methylthio)-2,2':6,2''-terpyridine: 2,2':6',2''-Terpyridine,

4'-(methylthio)- (9); (78570-35-1)

Nickel chloride hexahydrate: Nickelbischofite (9); (70330-51-7)

Sodium borohydride: Borate (1-), tetrahydro-, sodium (8,9); (16940-66-2)

**(S)-(+)-2-(p-TOLUENESULFINYL)-2-CYCLOPENTENONE: PRECURSOR FOR
ENANTIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED CYCLOPENTANONES
(2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-, (S)-)**



Submitted by Martin Hulce, John P. Mallamo, Leah L. Frye, Timothy P. Kogan, and Gary H. Posner.¹

Checked by Ernest B. Clark, Michel Crevoisier, Han-Young Kang, and Robert M. Coates.

1. Procedure

Caution! Part A should be conducted in an efficient fume hood to avoid exposure to sulfur dioxide generated in the reaction.

A. *(S)-(-)-Menthyl p-toluenesulfinate.* In a dry, 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet are placed a magnetic

stirring bar and 65 g (40 mL, 0.55 mol) of thionyl chloride (Note 1). The liquid is stirred under a nitrogen atmosphere as 35.6 g (0.200 mol) of anhydrous sodium p-toluenesulfinate (Note 2) is added in portions over about 1 hr (Note 3). The solution immediately develops a yellow-green tinge as sulfur dioxide is liberated. After about three-fourths of the sulfinate has been added, 30 mL of benzene is added to facilitate stirring. The greenish slurry is stirred for another 1.5 hr, after which 75 mL of benzene is added. The mixture is transferred to a 500-mL, round-bottomed flask, along with 75 mL of benzene used to rinse the flask. Excess thionyl chloride and benzene are removed by rotary evaporation and gentle heating. Four 150-mL portions of benzene are added to the residue, and each portion is evaporated to complete the removal of the thionyl chloride. The flask is equipped with a magnetic stirring bar and a 125-mL, pressure-equalizing dropping funnel. The crude p-toluenesulfinyl chloride, sodium chloride, and residual benzene are dissolved in 150 mL of anhydrous diethyl ether. The resulting ethereal suspension is stirred and cooled in an ice bath as 31.3 g (0.200 mol) of (-)-menthol (Note 1) in 25 mL of pyridine is added over ca. 2 min. The mixture is allowed to stir overnight after which 70 g of ice is added. The layers are separated and the aqueous layer is extracted with one 100-mL portion of ether. The ethereal solutions are combined, washed three times with 50-mL portions of 20% aqueous hydrochloric acid, and dried with a mixture of anhydrous sodium sulfate and potassium carbonate. Filtration to separate the drying agents and rotary evaporation until a pressure of 3 mm is sustained leaves 57.5 g of crude menthyl p-toluenesulfinate as a clear liquid admixed with white crystals. The less soluble (S)-(-) diastereomer (1) is isolated in several crops by crystallization from 1.2 volumes of reagent-grade acetone at -20°C. After the first crop has been collected, 3 drops of concd hydrochloric acid is added to

the acetone mother liquor to effect equilibration of the sulfinate diastereomers. A total of 40.9-42.2 g of crystalline sulfinate is obtained in six crops. Recrystallization from acetone affords two crops of (S)-(-)-menthyl p-toluenesulfinate, mp 105-106°C, $[\alpha]_D^{25}$ -199.4 (acetone, d 1.5), weighing 36.9-38.2 g (63-65%) (Note 4).

B. (S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal. A 250-mL, three-necked, round-bottomed flask equipped with two rubber septa, a nitrogen inlet, 125-mL pressure-equalizing dropping funnel, and a magnetic stirring bar is flame dried under nitrogen. After the apparatus cools to room temperature, the flask is charged with 70 mL of anhydrous tetrahydrofuran (Note 5) and cooled in an isopropyl alcohol-dry ice bath. Stirring is begun as 42 mL (60.8 mmol) of 1.45 M butyllithium in hexane (Note 6) is added slowly through the dropping funnel over 10-30 min. After another 10 min a solution of 11.3 g (55.1 mmol) of 2-bromo-2-cyclopentenone ethylene ketal (Note 7) is added from the dropping funnel over 30 min. The colorless or pale yellow solution is stirred and cooled at -78°C for 1.5 hr. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, two rubber septa and a stopcock connected to a bubbler gas exit is flushed with nitrogen and charged with 24.4 g (82.9 mmol) of (S)-(-)-menthyl p-toluenesulfinate and 460 mL of anhydrous tetrahydrofuran. The sulfinate suspension is stirred vigorously (Note 8) and cooled at -78°C as the vinyl lithium reagent (2) in the first flask is then transferred into the second flask through a cooled cannula by means of nitrogen pressure (Note 9). As the 50-min transfer proceeds, the sulfinate suspension becomes yellow. The mixture is stirred for another 15 min at -78°C, the cooling bath is removed, and 125 mL of saturated aqueous sodium dihydrogen phosphate is added. When the contents have warmed to room temperature, the tetrahydrofuran is removed by rotary evaporation. The

residue is partitioned between 300 mL of water and 200 mL of chloroform. The aqueous layer is extracted with three 100-mL portions of chloroform. The chloroform extracts are combined and dried over anhydrous potassium carbonate. Filtration of the drying agent and evaporation of the chloroform gives 40-55 g of a viscous brown oil consisting of the sulfinyl ketal, menthol, menthyl sulfinat, minor by-products, and residual chloroform. The sulfinyl ketal is isolated by modified flash chromatography on 500 g of Woelm silica gel (32-64 μ) packed in dry diethyl ether in a 6.5 cm x 45 cm column (Note 10). The crude product is applied to the column in 25 mL of chloroform and the column is eluted with ether under sufficient compressed air pressure to achieve a flow rate of 60 mL per min. After thirty 60-mL fractions are collected, the solvent is changed to ethyl acetate, and another forty 60-mL fractions are collected and analyzed by thin-layer chromatography (Note 11). Combination and evaporation of fractions 40-60 provides 9.05-9.75 g (62-67%) of crude (S)-(+)-2-(p-toluenesulfinyl)-2-cyclopentenone ethylene ketal as a pale, yellow oil, $[\alpha]_D^{25} +78^\circ$ (CHCl_3 , c 0.25) (Note 12).

C. (S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone. A magnetic stirring bar, 100 g of anhydrous copper(II) sulfate, and a solution of 9.05-9.75 g of the sulfinyl ketal in 300 mL of acetone are placed in a 500-mL Erlenmeyer flask. The flask is flushed with nitrogen and stoppered. The suspension is stirred vigorously overnight, the copper sulfate is separated by filtration, and the filter cake is washed thoroughly with 500-700 mL of acetone. Concentration of the combined filtrates by rotary evaporation gives 7.36-7.58 g of tan crystals. Recrystallization is carried out by dissolving the product in a minimum volume of ethyl acetate (ca. 80 mL) at room temperature, treating with Norite, diluting with an equal volume of diethyl ether, and cooling to -20°C . After the resulting crystals are collected, the mother liquor is

evaporated under reduced pressure at room temperature, and the procedure is repeated twice. The mother liquor is again evaporated and the residue (1.4-1.8 g) is purified by flash chromatography on 110 g of Woelm silica gel using ethyl acetate as eluant (Note 13). Combination of appropriate fractions, evaporation, and recrystallization affords two additional crops of crystalline product (0.4-0.7 g). The yield of (S)-(+)-2-(p-toluenesulfinyl)-2-cyclopentenone, mp 125-126°C, $[\alpha]_D^{25} +148^\circ$ (CHCl₃, *c* 0.11), is 6.02-6.60 g (50-54% based on bromo ketal) (Notes 14 and 15).

2. Notes

1. This reagent was purchased from Aldrich Chemical Company, Inc.

2. Sodium p-toluenesulfinate hydrate purchased from Aldrich Chemical Company, Inc., was dried overnight in a vacuum oven at 140°C to remove the water of hydration. The weight loss amounts to 19-21%.

3. The checkers added the sodium sulfinate from a 100-mL, three-necked flask via a bent sidearm fitted to the reaction vessel. A stream of nitrogen flowing through the 100-mL flask prevented backflow of fumes from the reaction and caking of the sodium sulfinate powder.

4. Aldrich Chemical Company, Inc. is now preparing for sale the (S)-(-)- and the (R)-(+)-menthyl p-toluenesulfonates. The spectral properties of the (S)-(-) sulfinate are as follows: IR (CCl₄) cm⁻¹: 2958 (s), 2924 (s), 2870 (s), 1455 (m), 1135 (s), 961 (s), 919 (s), 853 (s); ¹H NMR (90 MHz, CDCl₃) δ : 0.72 (d, 3 H, J = 6, CHCH₃), 0.94 and 0.86 (2 d, 6 H, J = 7, CH(CH₃)₂), 2.37 (s, 3 H, ArCH₃), 4.08 (t of d, 1 H, J = 5, 10, CHOSO₂), 7.26 and 7.56 (2 d, 4 H, J = 8, ArH).

5. Tetrahydrofuran was dried by distillation from sodium-benzophenone ketyl before use.

6. Butyllithium in hexane is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton/Thiokol Inc. The reagent was titrated with anhydrous diphenylacetic acid as described in the literature.²

7. 2-Bromo-2-cyclopentenone ethylene ketal was prepared according to a published procedure.³ The compound is quite unstable and should be purified by distillation before use to remove impurities. The submitters stored the bromo ketal at -20°C over 3 Å molecular sieves and redistilled a portion in a Kugelrohr apparatus with an oven temperature of 38°C (0.1 mm) immediately before use. The checkers found it necessary to distill the bromo ketal a second time to increase its purity. The compound was stored at -20°C and used in Part B the next day.

8. The submitters caution that rapid stirring is essential to avoid local heating from the exothermic reaction, and as a consequence, diminished yields.

9. The checkers used a 61-cm, 16-gauge cannula with a single loop ca. 6 cm in diameter immersed in an isopropyl alcohol-dry ice bath. The submitters report that lower yields were obtained when the vinyl lithium reagent was allowed to warm above -78°C briefly during the transfer.

10. The submitters purified the product by medium pressure liquid chromatography on a 60-cm x 5-cm column packed with 230-400 mesh silica gel 60 purchased from E. Merck. Ethyl acetate was used as eluant at a flow rate of 4-10 mL per min. Fractions (20 mL) were collected and analyzed by thin layer chromatography.

11. Thin layer chromatograms were obtained with silica gel as absorbent and ethyl acetate as developing solvent. The order of elution and R_f values of the major components are as follows: menthyl sulfinate (0.65), menthol (0.59), sulfinyl ketal (0.30).

12. The ^1H NMR spectral characteristics of the ketal are as follows (CDCl_3) δ : 2.0-2.2 (m, 2 H, CH_2), 2.3-2.6 (m, 2 H, $\text{C}=\text{CCH}_2$), 2.37 (s, 3 H, CH_3), 3.7-3.9 (m, 4 H, $\text{OCH}_2\text{CH}_2\text{O}$), 6.67 (t, 1 H, $J = 2$, $\text{C}=\text{CH}$), 7.24 and 7.57 (2 d, 4 H, $J = 8$, aryl H).

13. Flash chromatography was carried out according to a procedure in the literature.⁴

14. The spectral properties of the sulfinyl enone are as follows: IR (CCl_4) cm^{-1} : 2924 (m), 1715 (s), 1287 (m), 1152 (s), 1083 (s), 1054 (s), 728 (m); ^1H NMR (CDCl_3) δ : 2.2-2.5 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.6-2.8 (m, 2 H, $\text{C}=\text{CCH}_2$), 7.19 and 7.58 (2 d, 4 H, $J = 8$, aryl H), 8.03 (t, 1 H, $J = 2$, $\text{C}=\text{CH}$); mass spectrum (70 eV), m/z (rel intensity): 220 (M^+ , 30), 172 (100), 139 (48), 129 (72). The product was analyzed by the submitters: Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{SO}_2$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.53; H, 5.51; S, 14.72.

15. The submitters report that the sulfinyl ketone may be stored in vials in a desiccator at 0°C for more than 1 year without evidence of decomposition. Although storage under an inert atmosphere is not necessary, the checkers found that product exposed to the atmosphere at room temperature became discolored after several weeks.

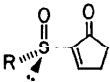
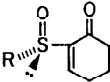
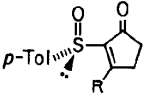
3. Discussion

Enantiomerically pure β -substituted carbonyl compounds serve as useful intermediates in the synthesis of many chiral organic compounds. The enantioselective synthesis of acyclic β -substituted carboxylic acids has been reported by Meyers,⁵ Mukaiyama,⁶ and Koga.⁷ However, no effective, general method for the enantio-controlled preparation of β -substituted cycloalkanones was available prior to the investigations by the submitters.⁸ For example, poor enantioselectivity was observed in conjugate additions of organometallic reagents to cyclic α,β -enones in the presence of optically active solvents⁹ or chiral ligands.¹⁰ In contrast, the submitters have found that conjugate addition to chiral cyclic α -sulfinyl α,β -enones occurs with high enantioselectivity.¹¹ Thus, the title compound is a useful intermediate for the synthesis of a variety of β -substituted cyclopentanones.

The preparation of (S)-(-)-menthyl p-toluenesulfinate described in Part A is based upon the procedure reported by Solladié.¹² 2-Bromo-2-cyclopentenone ethylene ketal is available from 2-cyclopentenone by the procedure of Smith and co-workers.³ The present procedure has been used by the submitters to prepared analogous chiral α -sulfinyl α,β -enones (Table I).¹¹ The utility of these chiral synthons is enhanced by their stability, the facility of their conjugate addition reactions, and the capability of producing either enantiomeric β -substituted adduct by varying the reaction conditions.¹³ Similar methodology has allowed conversion of some enantiomerically pure butenolide sulfoxides into the corresponding β -substituted butyrolactones.¹⁴

Both (S)-(-)- and (R)-(+)-menthyl 4-toluenesulfates are now available from the Aldrich Chemical Company, Inc.

TABLE I
ENANTIOMERICALLY PURE α -SULFINYL- α,β -ENONES PREPARED FROM
ETHYLENE KETALS OF α -BROMO- α,β -ENONES

Sulfinyl enone	R	Yield (%)	mp ($^{\circ}\text{C}$)	$[\alpha]_{\text{D}}^{25}$
	<i>p</i> -MeC ₆ H ₄	50-54	125-126	+142 $^{\circ}$
	1-naphthyl	65	96.5-97.0	+292 $^{\circ}$
	<i>p</i> -MeOC ₆ H ₄	76	120.5-121.5	+141 $^{\circ}$
	<i>p</i> -MeC ₆ H ₄	66	101-102	+210 $^{\circ}$
	Me	38	90.5-91.0	+21.0 $^{\circ}$
	<i>p</i> -MeC ₆ H ₄	35	132-133	-322 $^{\circ}$

1. Department of Chemistry, The John Hopkins University, Baltimore, MD 21218. Financial support from the National Science Foundation (CHE 79-15161) is gratefully acknowledged.
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Appendix

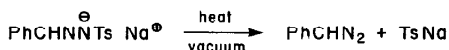
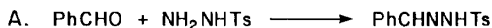
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

- (S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone: 2-Cyclopenten-1-one, 2-[(4-methylphenyl)sulfinyl]-. (S)- (9); (79681-26-8)
- (S)-(-)-Menthyl p-toluenesulfinate: Menthol, (-)-, (S)-p-toluenesulfinate, (-)- (8); Benzenesulfinic acid, 4-methyl-, 5-methyl-2-(1-methylethyl)-cyclohexyl ester, [1R-[1 α (S*), 2 β , 5 α]]- (9); (1517-82-4)
- Thionyl chloride (8,9); (7719-09-7)
- Sodium p-toluenesulfinate: p-Toluenesulfinic acid, sodium salt (8); Benzenesulfinic acid, 4-methyl-, sodium salt (9); (824-79-3)
- (-)-Menthol: Menthol, (-)- (8); Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1 α , 2 β , 5 α)]- (9); (2216-51-5)
- (S)-(+)-2-(p-Toluenesulfinyl)-2-cyclopentenone ethylene ketal: 1,4-Dioxaspiro[4.4]non-6-ene, 6-[(4-methylphenyl)sulfinyl]-, (S)- (10); (82136-15-0)
- Butyllithium: Lithium, butyl- (8,9); (109-72-8)
- 2-Bromo-2-cyclopentenone ethylene ketal: 1,4-Dioxaspiro[4.4]non-6-ene, 6-bromo- (9); (68241-78-1)
- Copper(II) sulfate: Sulfuric acid copper(2+) salt (1:1) (9); (7758-98-7)

TOSYLHYDRAZONE SALT PYROLYSES: PHENYLDIAZOMETHANES

(Benzenes, diazomethyl-)



Submitted by Xavier Creary.¹

Checked by Weyton W. Tam, Kim F. Albizzati and Robert V. Stevens.

1. Procedure

Caution! Diazo compounds are presumed to be highly toxic and potentially explosive. All manipulations should be carried out in a hood. Although in numerous preparations we have never observed an explosion, all pyrolyses and distillations should routinely be carried out behind a safety shield.

A. *Benzaldehyde tosylhydrazone.* A 14.6-g sample (0.078 mol) of p-toluenesulfonylhydrazide (Note 1) was placed in a 125-mL Erlenmeyer flask and 25 mL of absolute methanol was added. The slurry was swirled as 7.50 g (0.071 mol) of freshly distilled benzaldehyde was added rapidly. A mildly exothermic reaction ensued and the p-toluenesulfonylhydrazide dissolved. Within a few minutes, the tosylhydrazone began to crystallize. After 15 min the mixture was cooled in an ice bath. The product was collected on a Büchner funnel,

washed with a small amount of cold methanol, and dried under an aspirator vacuum. The dry benzaldehyde tosylhydrazone, mp 124-125°C, weighed 16.97-18.19 g (87-93%) and was not further purified.

B. *Phenyldiazomethane (Vacuum pyrolysis method)*. In a 200-mL, single-necked, round-bottomed flask is placed 13.71 g (0.05 mol) of benzaldehyde tosylhydrazone. A 1.0 M solution (51 mL) of sodium methoxide in methanol (0.051 mol) (Note 2) is added via syringe and the mixture is swirled until dissolution is complete (Note 3). The methanol is then removed by rotary evaporator. The last traces of methanol are removed by evacuation of the flask at 0.1 mm for 2 hr. The solid tosylhydrazone salt is broken up with a spatula and the flask is fitted with a vacuum take-off adaptor and a 50-mL receiver flask. The system is evacuated at 0.1 mm and the receiver flask is cooled in a dry ice-acetone bath to about -50°C. The flask containing the salt is immersed in an oil bath and the temperature is raised to 90°C (use a safety shield). At this temperature, red phenyldiazomethane first begins to collect in the receiver flask. The temperature is raised to 220°C over a 1-hr period (Note 4). During this time red phenyldiazomethane collects in the receiver flask (Note 5). The pressure increases to 0.35 mm over the course of the pyrolysis. On completion of the pyrolysis the pressure drops to less than 0.1 mm.

The apparatus is disconnected and the 50-mL receiver flask which contains the crude phenyldiazomethane is fitted with a water-cooled short-path distillation head and a receiver flask cooled to about -50°C in a dry ice-acetone bath. The pressure is lowered to 1.5 mm and a trace of methanol collects in the receiver. A new receiver flask is connected and cooled to -50°C and the pressure is lowered to less than 0.2 mm. Red phenyldiazomethane distills below room temperature (Note 6). The yield of phenyldiazomethane,

which is a liquid above -30°C , is 4.50-4.70 g (76-80%). The product should be used immediately or stored at a low temperature (-20 to -80°C) under nitrogen or argon (Notes 7-11); it is explosive at room temperature.

2. Notes

1. p-Toluenesulfonylhydrazide was obtained from Aldrich Chemical Company, Inc. and used without further purification.

2. The sodium methoxide solution was prepared by dissolving 2.30 g of sodium in absolute methanol and diluting it to 100 mL. If commercial sodium methoxide powder is used, it must be of high quality; otherwise the yield of phenyldiazomethane is lower.

3. Powdered sodium hydroxide can be used in place of sodium methoxide with no appreciable change in yield. Sodium hydroxide dissolves less readily in methanol.

4. When carried out on a small scale, pyrolysis is complete at lower temperatures (160° - 200°C)

5. Phenyldiazomethane solidifies at dry ice-temperature. Care must be taken not to plug the vacuum take-off adapter; this occurs if the temperature of the receiver flask is too low. The receiver bath was maintained manually at about -50°C by addition of small pieces of dry ice to an acetone bath. We prefer to use this procedure rather than a chloroform-dry ice bath which freezes at -63°C , because of the toxic nature of chloroform and the disposal problems associated with this solvent.

6. Slight warming with an oil bath at 30°C allows distillation to proceed at a reasonable rate. The bath should not be heated above this temperature. Gutsche and Jason² report a boiling point of 37 - 41°C at 1.5

mm. Although in numerous distillations we have never experienced any difficulty, Gutsche and Jason² report that phenyldiazomethane "sometimes detonated violently during purification..." by distillation. Therefore we emphatically recommend that distillation be carried out below room temperature, behind a safety shield. On completion of the distillation, only a small amount of non-volatile residue remained.

7. The checkers reported that a sample that was allowed to stand at room temperature for approximately 1 hr and then exposed to air decomposed violently after 5 min. In numerous preparations, when distilled phenyldiazomethane was immediately stored at -20°C or at -80°C under nitrogen, we never experienced any difficulty. We emphasize the need to keep phenyldiazomethane cold, and under nitrogen.

8. In runs on smaller scales, yields ranged from 84-91%.

9. The infrared spectrum (CCl₄) shows an intense band at 4.83 μ (2000 cm⁻¹); ¹H NMR (CCl₄) δ : 4.79 (s, 1 H), 6.7-7.6 (m, 5 H).

10. Phenyldiazomethane shows no appreciable change on storage at -80°C for 3 months. Storage at -20°C led to significant decomposition after 2 weeks.

11. Traces of diazo compounds should be destroyed by addition to acetic acid.

3. Discussion

Diazo compounds have previously been prepared by a variety of methods. Some of these methods include hydrazone oxidations,³ the reaction of diazomethane with acid chlorides,⁴ the reaction of activated methylene compounds with tosyl azide,⁵ decomposition of N-nitroso compounds,⁶ diazotization of amines,⁷ and pyrolysis of tosylhydrazone salts.⁸⁻¹³ The

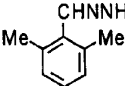
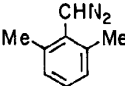
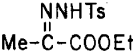
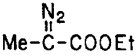
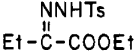
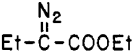
present procedure for the preparation of phenyldiazomethane illustrates the vacuum pyrolysis method introduced by Shechter¹² for carrying out the Bamford-Stevens reaction.⁹

Phenyldiazomethane has been prepared by reaction of base with ethyl N-nitroso-N-benzylcarbamate,¹³ N-nitroso-N-benzylurea¹⁴ and N-nitroso-N-benzyl-N'-nitroguanidine.¹⁵ Staudinger's preparation¹⁶ and that of Gutsche and Jason² employed mercuric oxide oxidation of benzaldehyde hydrazone. Yates and Shapiro¹⁷ prepared phenyldiazomethane by basic cleavage of azibenzil. Bamford and Stevens⁹ prepared phenyldiazomethane by solution pyrolysis of the salt of benzaldehyde tosylhydrazone. Closs and Moss¹⁰ and Farnum¹¹ used variations of this solution pyrolysis method for the preparation of phenyldiazomethane. The vacuum pyrolysis method employed by Shechter¹² has also been used to prepare phenyldiazomethane.

The present procedure uses sodium methoxide in methanol for generation of the tosylhydrazone salt. This procedure gives the highest reported yield and, unlike other procedures, also gives pure diazo compounds free from solvents. This vacuum pyrolysis method appears applicable to the formation of relatively volatile aryldiazomethanes from aromatic aldehydes. Table I gives yields of diazo compounds produced by this vacuum pyrolysis method. The yields have not been optimized. The relatively volatile diazo esters, ethyl α -diazopropionate¹⁸ and ethyl α -diazobutyrate can also be prepared by this method.

TABLE I

FORMATION OF DIAZO-COMPOUNDS BY VACUUM PYROLYSIS OF
SODIUM SALTS OF TOSYLHYDRAZONES

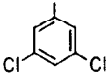
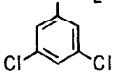
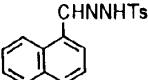

Tosylhydrazone	Product	Yield (%)
<i>p</i> -MeC ₆ H ₄ CHNNHTs	<i>p</i> -MeC ₆ H ₄ CHN ₂	52
<i>m</i> -MeC ₆ H ₄ CHNNHTs	<i>m</i> -MeC ₆ H ₄ CHN ₂	55
		69
<i>p</i> -FC ₆ H ₄ CHNNHTs	<i>p</i> -FC ₆ H ₄ CHN ₂	59
<i>m</i> -FC ₆ H ₄ CHNNHTs	<i>m</i> -FC ₆ H ₄ CHN ₂	84
		87
		65

The major limitation of the vacuum pyrolysis method appears to be thermal decomposition of less volatile diazo compounds during the pyrolysis. The vacuum pyrolysis method was unsuccessful for the preparation of 1-naphthyl diazomethane and 3,5-dichlorophenyldiazomethane. However, such diazo compounds could be prepared from the corresponding tosylhydrazone salts by pyrolysis in ethylene glycol and extraction of the aryl diazomethane into hexane or ether. This procedure, as described by Goh,¹⁹ permits the periodic extraction of the potentially labile diazo compound into an organic solvent while leaving the unreacted tosylhydrazone salt dissolved in the immiscible ethylene glycol phase. This solution pyrolysis method can also be used to prepare aryl diazo esters in high yields. This method is quite useful since the starting keto esters can be readily prepared in large quantities by reaction of the corresponding arylmagnesium bromides with diethyl oxalate.²⁰

In a typical procedure, 0.14 g of sodium was dissolved in 10 mL of ethylene glycol by heating to 70°C and 0.0041 mol of tosylhydrazone was added. After heating with vigorous stirring for 5 min at 70-80°C, the mixture was cooled to about 35°C and 15 mL of hexane or ether was added with continued stirring. The organic extract was removed by pipet and the procedure was repeated a total of 5 times. The combined organic extracts were washed with 30 mL of 5% sodium hydroxide solution, with a saturated sodium chloride solution, and dried over magnesium sulfate. After filtration, the solvent was removed on a rotary evaporator to leave the diazo compound. Table II gives yields of diazo compounds prepared by this solution pyrolysis method.

TABLE II

FORMATION OF DIAZO COMPOUNDS BY PYROLYSIS OF SODIUM SALTS OF
TOSYLHYDRAZONES IN ETHYLENE GLYCOL

Tosylhydrazone	Temperature (°C)	Product	Yield (%)
$p\text{-BrC}_6\text{H}_4\text{CHNNHTs}$	70 ^a	$p\text{-BrC}_6\text{H}_4\text{CHN}_2$	80
$p\text{-ClC}_6\text{H}_4\text{CHNNHTs}$	80 ^a	$p\text{-ClC}_6\text{H}_4\text{CHN}_2$	71
$m\text{-CF}_3\text{C}_6\text{H}_4\text{CHNNHTs}$	80 ^a	$m\text{-CF}_3\text{C}_6\text{H}_4\text{CHN}_2$	79 ^c
$p\text{-CF}_3\text{C}_6\text{H}_4\text{CHNNHTs}$	80 ^a	$p\text{-CF}_3\text{C}_6\text{H}_4\text{CHN}_2$	88 ^c
$m\text{-NCC}_6\text{H}_4\text{CHNNHTs}$	80 ^b	$m\text{-NCC}_6\text{H}_4\text{CHN}_2$	45
$p\text{-NCC}_6\text{H}_4\text{CHNNHTs}$	80 ^b	$p\text{-NCC}_6\text{H}_4\text{CHN}_2$	63
$m\text{-NO}_2\text{C}_6\text{H}_4\text{CHNNHTs}$	65 ^b	$m\text{-NO}_2\text{C}_6\text{H}_4\text{CHN}_2$	56
	80 ^a		90
	80 ^a		77
$\text{Ph}-\overset{\text{NNHTs}}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	70 ^b	$\text{Ph}-\overset{\text{N}_2}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	86
$p\text{-MeC}_6\text{H}_4-\overset{\text{NNHTs}}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	70 ^b	$p\text{-MeC}_6\text{H}_4-\overset{\text{N}_2}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	88
$p\text{-MeOC}_6\text{H}_4-\overset{\text{NNHTs}}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	70 ^b	$p\text{-MeOC}_6\text{H}_4-\overset{\text{N}_2}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	76
$m\text{-CF}_3\text{C}_6\text{H}_4-\overset{\text{NNHTs}}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	70 ^b	$m\text{-CF}_3\text{C}_6\text{H}_4-\overset{\text{N}_2}{\underset{\text{ }}{\text{C}}}-\text{COOEt}$	94

^aThe salt in ethylene glycol was heated at this temperature, cooled, and extracted periodically with hexane.

^bEther extraction.

^cThis product was further purified by distillation at less than 0.1 mm. The other products were not distilled.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Phenyldiazomethane: Toluene, α -dialzo- (8); Benzene, diazomethyl- (9);
(766-91-6)

Benzaldehyde tosylhydrazone: p-Toluenesulfonic acid benzylidenehydrazide (8);
Benzenesulfonic acid, 4-methyl-, (phenylmethylene) hydrazide (9); (1666-17-7)

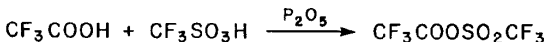
Benzaldehyde (8,9); (100-52-7)

p-Toluenesulfonylhydrazide: p-Toluenesulfonic acid hydrazide (8);

Benzenesulfonic acid, 4-methyl-, hydrazide (9); (1576-35-8)

TRIFLUOROACETYL TRIFLATE

(Acetic acid, trifluoro-, anhydride with trifluoromethanesulfonic acid)



Submitted by Stephen L. Taylor, T. R. Forbus, Jr., and J. C. Martin.¹

Checked by Thomas W. Panunto and Edwin Vedejs.

1. Procedure

Caution! The volatile product reacts rapidly with water to give corrosive strong acids. It also reacts rapidly with other nucleophiles. Care should therefore be exercised to avoid inhalation of its vapors. It should be handled in a well-vented fume hood.

In a 1-l flask containing 160 g (1.13 mol) of powdered phosphorus oxide (P_2O_5), thoroughly mixed with an equal volume of dried fine sand, is added a mixture of 85.5 g (0.75 mol) of trifluoroacetic acid (TFA) (Note 1) and 56.5 g (0.750 mol) of triflic acid (TfOH) at -20°C (Note 2). The stoppered flask (Note 3) is vigorously shaken for 5 min and then fitted for simple distillation, with the receiving flask cooled to -78°C , and allowed to stand at room temperature under a dry nitrogen atmosphere for 2.5 hr. The liquid is removed from the solid mixture by simple distillation at a bath temperature of 240°C (Note 4) for 3.5 hr (Note 5). The distillate is then carefully fractionally distilled (Note 6) from 5 g of powdered P_2O_5 (Note 7) with the receiving flasks cooled to -78°C . The colorless liquid collected at $62.5\text{--}63^\circ\text{C}$ (760 mm)

(Note 8), 69 g (75%) of trifluoroacetyl triflate (TFAT), is of 99% purity (Note 9), as determined by fluorine magnetic resonance (Note 10).

2. Notes

1. The 99% TFA obtained from Aldrich Chemical Company, Inc., was used without further purification.

2. Triflic acid (TfOH) obtained from Minnesota Mining & Manufacturing Company, (3M), in kilogram quantities was used without further purification.

3. Ground glass joints were connected using Teflon sleeves or a chlorofluorocarbon stopcock grease.

4. High temperatures are needed to distill the products from P_2O_5 . The use of temperatures higher than $250^{\circ}C$, however, causes the round-bottom flask to break when the temperature is lowered to near room temperature. Upon completion of the reaction, the P_2O_5 sand mixture can be removed from the flask by careful, slow addition of water. The checkers used an equilibrated bath of sand in a large heating mantle; the flask always broke after distillation.

5. The nitrogen outlet from the distillation apparatus should be well vented.

6. An 8-mm x 1-m jacketed column packed with a coiled tantalum wire was used by the submitters. The checkers used a Vigreux column of similar size.

7. Since the distillate contains 1-3% of the starting acids, P_2O_5 is added to prevent the reaction of TFA and TFAT, which gives trifluoroacetic anhydride (TFAA) and TfOH.

8. The first fraction is TFAA, bp $38.5-41^{\circ}C$ (760 mm).

9. The impurity is TFAA.

10. The reactants and products show only singlets in their fluorine magnetic resonance spectra with the following chemical shifts (downfield from fluorotrichloromethane internal standard) δ : TFA, -76.3; TfOH, -77.3; TFAT, -73.3 and -74.8; TFAA, -75.9; triflic anhydride, -72.6 ppm.

3. Discussion

Trifluoroacetyl triflate is probably the most powerful trifluoroacetylating agent known, as evidenced by its reactivity toward several types of nucleophiles under mild conditions. A sterically hindered base, 2,6-di-*tert*-butyl-4-methylpyridine,² may be used to scavenge the triflic acid produced in the reactions, since it does not react with TFAT under these conditions.

Trifluoroacetylation occurs at carbon in activated arenes such as anthracene³ under milder conditions using TFAT than when using TFAA. Trifluoroacetate esters are formed from alcohols and phenols,⁴ while ketones are acylated at oxygen to yield enol trifluoroacetates.³ Amines⁴ give the corresponding amides upon reaction with one equivalent of TFAT or imides upon reaction with two equivalents. Some covalent halides (fluorides⁵ and chlorides³) are acylated at halogen by TFAT to yield the very volatile trifluoroacetyl halides and ionic triflates. It was recently reported that TFAT reacts with a thioketone to give a stable cation.⁶ Reaction of TFAT with the methyl ester of glutaconic acid gives 2,6-dimethoxy pyrylium triflate, the first member of a new class of pyrylium salts⁴ with alkoxy groups at positions 2 and 6.

The high reactivity of TFAT limits the number of solvents that can be used for its reactions. We have found that TFAT is unreactive toward saturated hydrocarbons, benzene, and common halogenated solvents. It reacts only very slowly with nitromethane, but reacts relatively rapidly with tetrahydrofuran, ethyl acetate, and acetonitrile.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Numbers)

Trifluoroacetyl triflate: Acetic acid, trifluoro-, anhydride with trifluoromethanesulfonic acid (9); (68602-57-3)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

Triflic acid: Methanesulfonic acid, trifluoro- (8,9); (1493-13-6)

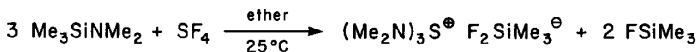
Phosphorus oxide (8,9); (1314-56-3)

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride (8,9); (407-25-0)

Triflic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

TRIS(DIMETHYLAMINO)SULFONIUM DIFLUOROTRIMETHYLSILICATE

(Sulfur(1+), tris(N-methylmethanaminato)-, difluorotrimethylsilicate(1-))



Submitted by William J. Middleton.¹

Checked by Fred G. West and Edwin Vedejs.

1. Procedure

Caution! This procedure should be conducted in an efficient hood to avoid exposure to the toxic gas sulfur tetrafluoride.

A dry, 500-mL, four-necked flask equipped with a magnetic stirrer, dry-ice condenser, thermometer (-100° - 50°C) and a gas inlet tube is assembled as shown in Figure 1. The system is flushed with nitrogen through three-way stopcocks A and B, the four-necked flask is charged with 150 mL of dry ether (Note 1), and the dropping funnel is charged with 46.9 g (0.40 mol) of N,N-dimethylaminotrimethylsilane (Note 2). The reaction vessel is maintained under a positive nitrogen pressure using a bypass nitrogen stream and bubbler. Stopcock A is connected to the sulfur tetrafluoride (SF₄) tank (Note 3) and stopcock B is turned to vent directly into a nitrogen bypass line and bubbler. While the graduated cylinder C is cooled in acetone-dry ice, SF₄ is slowly passed into the cylinder until 7 mL (13 g at -70°C, 0.12 mol) of liquid SF₄ have condensed. Stopcock A is closed and B is vented directly into the three-necked flask. Removal of the cooling bath from graduated cylinder C allows distillation of SF₄ into the cooled reaction vessel.

2. Notes

1. It is important that the ether be very dry (distilled from Na-benzophenone). Otherwise, the quality of the product and the yield will be substantially lower.

2. N,N-Dimethylaminotrimethylsilane is available from Petrarch Systems, Inc. Care should be taken to assure that there is no free dimethylamine present. Commercial samples can be purified by distillation through a 6"-Vigreux column, bp 86-87°C. The submitters used a spinning band column for removal of hexamethyldisiloxane, bp 99-100°C, which is present as a contaminant.

3. Sulfur tetrafluoride is available from Air Products and Chemicals, Inc. or Matheson Gas Products. Commercial SF₄ was used without purification.

4. The submitters obtained good yields without a glove bag, but the checkers encountered 30-40% yield reduction without this precaution. A dry box is also suitable.

5. Because tris(dimethylamino)sulfonium difluorotrimethylsilicate is very hygroscopic, it is best transferred in a dry atmosphere of nitrogen or argon (dry box or glove bag).

6. A brief exposure to moist air will appreciably lower the melting point. A melting point as low as 58-62°C can be obtained.

3. Discussion

Tris(dimethylamino)sulfonium difluorotrimethylsilicate is a source of soluble organic fluoride ion of high anionic reactivity. Fluoride ion from this salt and other tris(dialkylamino)sulfonium difluorotrimethylsilicates has

been used to displace halogen from carbon² and to cleave Si-O³⁻⁷ and Si-C=O^{7,8} bonds. Since these salts can be prepared in a rigorously anhydrous state, they have an advantage over quaternary ammonium fluorides which usually contain some water. Tris(dialkylamino)sulfonium difluorotrimethylsilicates have also been used to prepare other sulfonium salts with high nucleophilic reactivity, including (R₂N)₃S⁺ enolates,⁶ phenoxide,⁵ cyanide, azides, and cyanates.²

This method has been used to prepare several different tris(dialkylamino)sulfonium difluorotrimethylsilicates, including salts with greater organic solubility such as the tris(diethylamino)sulfonium^{2,3} and tris(pyrrolidine)sulfonium² difluorotrimethylsilicates. The tris(dimethylamino)sulfonium salt, however, is highly crystalline and thus has an advantage in ease of preparation and purification over these other salts.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tris(dimethylamino)sulfonium difluorotrimethylsilicate: Sulfur(1+), tris(N-methylmethanaminato)-, difluorotrimethylsilicate (1-) (9); (59218-87-0)

N,N-Dimethylaminotrimethylsilane: Silylamine, pentamethyl- (8,9); (2083-91-2)

Sulfur tetrafluoride: Sulfur fluoride (8,9); (7783-60-0)

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Division of the American Chemical Society. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons, Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60-64 will be included in a new five-year version of the collective volumes of *Organic Syntheses* which will appear as *Collective Volume Seven* in the traditional hard cover format, after the appearance of annual volume 64. It will be available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is adopted. For example, both diethyl ether and ethyl ether are normally used. Since ethyl ether is the established *Chemical Abstracts* name for the 8th Collective Index, it has been used in this volume. The 9th Collective Index name is 1,1'-oxybisethane, which the Editors consider too cumbersome.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

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Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

PREFACE

This volume reflects intensive activity in several areas of synthetic organic chemistry. The volume begins with enol/carbonyl condensations and several variants for synthesis of 5-membered carbocycles. Next comes a series of examples illustrating the synthesis of alkynes, alkenes, and aromatic carbocycles. Heteroelement chemistry is featured in the extensive use of organosilicon reagents, in several applications of transition element chemistry, in reactive nitrogen intermediates, and in the preparation of β -lactams, indoles, and other heterocycles. The last and largest section of the volume deals with a variety of chiral auxiliaries which are important in asymmetric synthesis. This field is in the midst of explosive growth and will undoubtedly see major changes and improvements in techniques and results over the next decade.

I would like to thank Carole Klingbeil, Joyce Bohling, and Professor Jeremiah P. Freeman and his office staff for their extensive help and patience in the preparation of text for this volume. Mr. P. Kierkus deserves credit for the structures, drawn with the ChemDraw™ program and for transforming a great deal of rough copy into final diagrams. Lastly, my thanks to those of my students over the past several years who have spent their time and energy checking procedures and contributing in other ways which left me time for this volume.

E. VEDEJS

*Madison, Wisconsin
January 1987*

A. HAROLD BLATT

January 9, 1903–March 19, 1986

A. Harold Blatt, second Secretary to the Board of Editors of *Organic Syntheses, Inc.*, 1938-1943, and co-editor with Henry Gilman of the revised edition of Collective Volume 1 of *Organic Syntheses*, passed away on March 19, 1986 in Melbourne, Florida at the age of 83.

Dr. Blatt was born in Cincinnati, Ohio and received B.S., M.A., and Ph.D. degrees from Harvard University in 1923-1926. He held post-doctoral positions at the College de France in Paris, Harvard University, and the University of Buffalo before he joined the faculty at Howard University as an associate professor in 1932. He became a member of the newly-formed Queens College in 1939, where he was a professor, and stayed for 32 years. His academic pursuits were interrupted during World War II when he was a Science Liaison Officer, the London Mission, in the Office of Scientific Research and Development (1944-1945), and a Technical Aide to Division 8 during the latter year.

Dr. Blatt also edited Collective Volume 2 of *Organic Syntheses* (1943), and served for many years on the Board of Directors, where his expertise and knowledge of finance were of inestimable value. At corporation meetings, his versatility was shown by the skill he demonstrated in the selection of the dinner wines. His editorial expertise was used also by Organic Reactions, Inc. where he was a member of the Editorial Board (1948-1954), and then served on the Advisory Board until 1986.

Dr. Blatt's teaching and research activities covered the period from his Harvard days into the 1980's. He was a co-editor with James B. Conant of the well-known text, *The Chemistry of Organic Compounds*, 3rd edition, which was published in 1947, and used widely during the 1950's. The text offered a new approach for organic chemistry students to the subjects of reaction rates and equilibria. It also presented new physico-chemical concepts and data, as well as an effort to cover some of the major topics of biochemistry and pharmacology, and relate their chemistry to the principles expounded in the book.

Harold Blatt served for three terms as chairman of the Chemistry Department at Queens College beginning in 1961, retired in 1971, and then moved to Melbourne, Florida where he was a member of the Chemistry Department at the Florida Institute of Technology.

Dr. Joel H. Blatt, his son, and a sister survive Dr. Blatt.

NORMAN RABJOHN

September 19, 1986

CONTENTS

Nigel D. A. Walshe, Graham B. T. Goodwin, Graham C. Smith, and Frank E. Woodward	1	ACETONE TRIMETHYLSILYL ENOL ETHER
Teruaki Mukaiyama and Koichi Narasaka	6	3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE BY CROSSED ALDOL REACTION
Koichi Narasaka	12	3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE
Eiichi Nakamura and Isao Kuwajima	17	RING EXPANSION AND CLEAVAGE OF SUCCINOIN DERIVATIVES: SPIRO[4.5]DECANE-1,4-DIONE AND ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE
H. Stetter, H. Kuhlmann and W. Haese	26	THE STETTER REACTION: 3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE (DIHYDROJASMONE)
Dale L. Boger, Christine E. Brotherton, and Gunda I. Georg	32	PREPARATION AND THREE-CARBON + TWO-CARBON CYCLOADDITION OF A CYCLOPROPENONE KETAL: CYCLOPROPENONE 1,3-PROPANEDIOL KETAL
Richard S. Threlkel, John E. Bercaw, Paul F. Seidler, Jeffrey M. Stryker, and Robert G. Bergman	42	1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE
M. Olomucki and J. Y. Le Gall	47	ALKOXYCARBONYLATION OF PROPARGYL CHLORIDE: METHYL 4-CHLORO-2-BUTYNOATE
Graham E. Jones, David A. Kendrick, and Andrew B. Holmes	52	1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE
Andrew B. Holmes and Chris N. Sporikou	61	TRIMETHYLSILYLACETYLENE
Anna Bou, Miquel A. Pericàs, Antoni Riera and Fèlix Serratosa	68	DIALKOXYACETYLENES: DI-tert-BUTOXYETHYNE, A VALUABLE SYNTHETIC INTERMEDIATE
Luciano Lombardo	81	METHYLENATION OF CARBONYL COMPOUNDS: (+)-3-METHYLENE-cis-p-MENTHANE

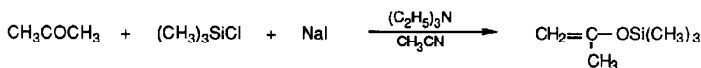
Eric Block and Mohammad Aslamb	90	A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF CONJUGATED DIENES FROM OLEFINS USING BROMOMETHANESULFONYL BROMIDE: 1,2-DIMETHYLENECYCLOHEXANE
Dale L. Boger and Michael D. Mullican	98	PREPARATION AND INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF AN ELECTRON-DEFICIENT DIENE: METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2H-1-BENZOPYRAN-3-CARBOXYLATE
F. E. Ziegler, K. W. Fowler, W. B. Rodgers, and R. T. Wester	108	AMBIENT TEMPERATURE ULLMANN REACTION: 4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE
Steven K. Davidsen, Gerald W. Phillips, and Stephen F. Martin	119	GEMINAL ACYLATION-ALKYLATION AT A CARBONYL CENTER USING DIETHYL N-BENZYLIDENAMINOMETHYLPHOSPHONATE: PREPARATION OF 2-METHYL-2-PHENYL-4-PENTENAL
Stuart J. Mickel, and modified by Chi-Nung Hsiao and Marvin J. Miller	135	4-ACETOXYAZETIDIN-2-ONE: SYNTHESIS OF A KEY BETA-LACTAM INTERMEDIATE BY A [2 + 2] CYCLOADDITION ROUTE
Louis S. Hegedus, Michael A. McGuire, and Lisa M. Schultze	140	1,3-DIMETHYL-3-METHOXY-4-PHENYL-AZETIDINONE
Jan Bergman and Peter Sand	146	4-NITROINDOLE
J. Buter and Richard M. Kellogg	150	SYNTHESIS OF MACROCYCLIC SULFIDES USING CESIUM THIOLATES: 1,4,8,11-TETRATHIACYCLOTETRADECANE
Günter Kresze, Hans Braxmeier, and Heribert Münsterer	159	ALLYLCARBAMATES BY THE AZA-ENE REACTION: METHYL N-(2-METHYL-2-BUTENYL)CARBAMATE
E. J. Corey and Andrew W. Gross	166	tert-BUTYL-tert-OCTYLAMINE
Dieter Enders, Peter Fey, and Helmut Kipphardt	173	(S)-(-)-1-AMINO-2-METHOXYMETHYL-PYRROLIDINE (SAMP) AND (R)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP), VERSATILE CHIRAL AUXILIARIES
Dieter Enders, Helmut Kipphardt, and Peter Fey	183	ASYMMETRIC SYNTHESSES USING THE SAMP-/RAMP-HYDRAZONE METHOD: (S)-(+)-4-METHYL-3-HEPTANONE
Oswald Ort	203	(-)-8-PHENYLMENTHOL

Ernest L. Eliel, Joseph E. Lynch, Fumitaka Kume, and Stephen V. Frye	215	CHIRAL 1,3-OXATHIANE FROM (+)- PULEGONE: HEXAHYDRO-4,4,7- TRIMETHYL-4H-1,3-BENZOXATHIIN
Charles A. Brown and Prabhakar K. Jadhav	224	(-)- α -PINENE BY ISOMERIZATION OF (-)- β -PINENE
Rena Imwinkelried, Martin Schiess, and Dieter Seebach	230	DIISOPROPYL (2S,3S)-2,3-O- ISOPROPYLIDENETARTRATE
Bernd Giese, J. Dupuis, and Marianne Nix	236	1-DEOXY-2,3,4,6-TETRA-O-ACETYL- 1-(2-CYANOETHYL)- α -D-GLUCOPYRANOSE
S. Hanessian	243	6-BROMO-6-DEOXY HEXOSE DERIVATIVES BY RING-OPENING OF BENZYLIDENE ACETALS WITH N-BROMOSUCCINIMIDE: METHYL 4-O-BENZOYL-6-BROMO-6-DEOXY- α -D-GLUCOPYRANOSIDE
Unchecked Procedures	251	
Cumulative Author Index for Volume 65	256	
Cumulative Subject Index for Volume 66	258	

ORGANIC SYNTHESSES

ACETONE TRIMETHYLSILYL ENOL ETHER

(Silane, trimethyl[(1-methylethenyl)oxy]-)



Submitted by Nigel D. A. Walshe, Graham B. T. Goodwin, Graham C. Smith,
and Frank E. Woodward.¹

Checked by V. A. Palaniswamy and James D. White.

1. Procedure

To a 5-L, four-necked flask, equipped with a mechanical stirrer, reflux condenser with nitrogen inlet, thermometer and pressure-equalizing dropping funnel, are added 150 g (2.6 mol) of acetone (Note 1) and 192 g (1.9 mol) of triethylamine (Note 2) under a nitrogen atmosphere. To this mixture, stirred at room temperature under nitrogen, is added via the dropping funnel 200 g (1.84 mol) of chlorotrimethylsilane over 10 min (Note 3). The flask is then immersed in a waterbath and the contents are warmed to 35°C. The waterbath is removed and the dropping funnel is charged with a solution of 285 g (1.9 mol) of sodium iodide (Note 4) in 2.14 L of acetonitrile (Note 5). This solution is added to the stirred mixture in the flask at such a rate that the temperature of the reaction is maintained at 35-40°C without external heating or cooling (Note 6). The addition requires approximately 1 hr. When addition is complete, the reaction mixture is stirred for a further 2 hr at room temperature. The contents of the flask are then poured into 5 L of ice-cold water, and the aqueous mixture is extracted with two 1-L portions of pentane

and once with 500 mL of pentane. The combined pentane extracts are dried over anhydrous potassium carbonate, and filtered into a 3-L, round-bottomed flask. This is arranged for distillation at atmospheric pressure, incorporating a 30-cm Vigreux fractionating column. The pentane is distilled off at atmospheric pressure, until a head temperature of 88°C is attained. The crude material is transferred to a 500-mL flask, and the product is then distilled at atmospheric pressure through a 20-cm Vigreux column. A forerun of 20 g is collected between room temperature and 94°C. The product is the fraction boiling at 94-96°C, the yield of which is 116-130 g (48-54%) (Note 7).

2. Notes

1. "AnalaR" grade acetone, as supplied by BDH, was used.
2. Triethylamine was dried over potassium hydroxide pellets for at least 24 hr.
3. Commercial chlorotrimethylsilane was used without purification. When it was added to the acetone/triethylamine mixture, only a very mild exothermic reaction occurred (ca. 2°C). Dense white fumes formed, and a turbid solution was obtained.
4. Sodium iodide was reagent grade. It is essential to dry this material thoroughly. Heating at 140°C for 8 hr under reduced pressure (ca. 20 mm) is satisfactory. The loss of weight on drying is roughly 5%. If this is not done, hexamethyldisiloxane is the principal product.
5. Acetonitrile was reagent grade, dried by passage through 1 kg of neutral alumina (grade 1), and then stored over 3 Å molecular sieves.

6. A copious white precipitate forms at this stage. If the reaction is not mildly exothermic, then very poor yields of product are obtained.

7. The yield is based on chlorotrimethylsilane. Two small-scale runs - 0.124 mol and 0.37 mol, also based on chlorotrimethylsilane - gave yields of 60% and 61%, respectively, which the submitters also reported on the larger scale. The material from the large-scale run was 92% pure by gas-chromatographic analysis. The impurities, identified by NMR, are triethylamine (0.5%) and hexamethyldisiloxane (7.5%). The product has the following spectral characteristics; IR (film) cm^{-1} : 1650, 1280, 1260, 1050; ^1H NMR (CDCl_3) δ : 0.13 (s, 9 H, SiCH_3), 1.69 (br s, 3 H, $=\text{CCH}_3$), 3.92 (m, 2 H, $=\text{CH}_2$).

3. Discussion

Trimethylsilyl enolates of aldehydes and ketones are now established as highly useful synthetic intermediates.² In particular, their Lewis acid-catalyzed reactions - e.g., alkylation³ and mild, regiospecific aldol condensations⁴ - provide useful alternatives to classical, base-generated metal enolate chemistry. This new methodology would be ideal for the introduction of the commonly-encountered acetyl residue. However the required silyl enol ether of acetone is not commercially available, nor is a simple, reliable and economical synthesis adequately described in the literature. The above procedure is an adaptation of a literature method,⁵ and relies on the generation of iodotrimethylsilane in situ. We have found that the precautions described in Notes 4 and 6 are crucial to the success of the preparation. This procedure makes available a useful reagent by a cheap, reliable route, starting from readily available materials, and in large or

small quantity. The trimethylsilyl enol ether of acetone has been prepared previously in good yield by reaction of acetone with trimethylsilyl triflate and triethylamine.⁶ However, the silyl triflate reagent is expensive for large-scale work. Another route⁷ involves the mercuric iodide-catalyzed rearrangement of α -trimethylsilylacetone (obtained from trimethylsilylmethylmagnesium chloride and acetic anhydride). This is a laborious, low-yield process. Other methods include a synthesis from acetone, chlorotrimethylsilane, and triethylamine⁸ (yields and exact procedure unspecified); or reaction of acetone with hexamethyldisilazane,⁹ or bis(trimethylsilyl)acetamide,¹⁰ and a catalytic amount of sodium in the presence of hexamethylphosphoric triamide. Two authors¹¹ who used the method of House¹² (no experimental details supplied) note that their product always contained about 30% of hexamethyldisiloxane, which could not be separated by fractional distillation.

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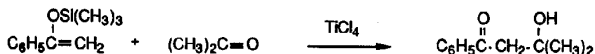
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Acetone trimethylsilyl enol ether: Silane, (isopropenyloxy)trimethyl- (8);
 Silane, trimethyl[(1-methylethenyl)oxy]- (9); (1833-53-0)
 Acetone (8); 2-Propanone (9); (67-64-1)
 Triethylamine (8): Ethanamine, N,N-diethyl- (9); (121-44-8)
 Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE BY CROSSED ALDOL REACTION

(1-Butanone, 3-hydroxy-3-methyl-1-phenyl-)



Submitted by Teruaki Mukaiyama and Koichi Narasaka.¹

Checked by Kathleen Hug and Clayton H. Heathcock.

1. Procedure

A 500-mL, three-necked flask is fitted with a stirring bar, rubber stopper, 100-mL pressure-equalizing dropping funnel and a three-way stop-cock which is equipped with a balloon of argon gas (Note 1). The flask is charged with 140 mL of dry methylene chloride (Note 2) and cooled in an ice bath. Titanium tetrachloride (11.0 mL) (Note 3) is added by a syringe with stirring by a magnetic stirrer, and a solution of 6.5 g of acetone in 30 mL of methylene chloride is added dropwise over a 5-min period. On completion of this addition a solution of 19.2 g of 1-phenyl-1-trimethylsiloxyethylene (Note 4) in 15 mL of methylene chloride (Note 5) is added dropwise over a 10-min period, and the mixture is stirred for 15 min.

The reaction mixture is poured into 200 mL of ice water with vigorous stirring and the organic layer is separated. The aqueous layer is extracted with two 30-mL portions of methylene chloride. The combined methylene chloride extracts are washed with two 60-mL portions of a 1:1 mixture of saturated aqueous sodium bicarbonate and water, and then with brine. The methylene chloride solution is dried over sodium sulfate and the methylene chloride is removed using a rotary evaporator.

The residue is dissolved in 30 mL of benzene, and the solution is transferred to a chromatographic column (50 mm diameter) consisting of 600 mL of silica gel. The product is eluted sequentially with (A) 1 L of 4:1 (v/v) hexane:ethyl acetate, (B) 1.5 L of 2:1 (v/v) hexane:ethyl acetate (flash chromatography) (Note 6).

The initial ca. 900 mL of the eluent is discarded. Concentration of the later fractions (ca. 1.3 L) under reduced pressure yields an oil of the pure product (Note 7). The total yield is 12.2-12.8 g (70-74%).

2. Notes

1. All the apparatus should be oven-dried before use.

2. Methylene chloride was purified by distillation from phosphorus pentoxide, then from calcium hydride, and was stored over Molecular Sieves 4A.

3. Freshly distilled titanium tetrachloride (bp 152-153°C) was used. The checkers distilled the titanium tetrachloride from calcium hydride.

4. The silyl enol ether may be obtained from the Fluka Chemical Corp., 255 Oser Avenue, Hauppauge, NY 11788. Alternatively, it may be prepared by the following modification of the procedure of Walshe and co-workers.² The Walshe procedure is followed exactly with 36 g (0.30 mol) of acetophenone, 41.4 g (0.41 mol) of triethylamine, 43.2 g (0.40 mol) of chlorotrimethylsilane, 60 g (0.40 mol) of sodium iodide, and 350 mL of acetonitrile. After extraction, the organic layer is dried over potassium carbonate and then concentrated with a rotary evaporator under reduced pressure. The crude product is a mixture of 97% of the desired silyl enol ether and 3% of acetophenone, as shown by gas chromatography. The crude product is distilled in a Claisen flask at a pressure of about 40 mm. After a small forerun (ca. 3

g), 52.3 g (91%) of silyl enol ether, bp 124-125.5°C, is obtained. The purity of this material is approximately 98%, as judged by gas chromatography and ^1H NMR spectroscopy.

5. Submitters report using 60 mL of hexane.

6. 3-Hydroxy-3-methyl-1-phenyl-1-butanone is too unstable to be purified by distillation, and is decomposed to acetophenone and acetone.

7. The initial fractions are sometimes contaminated with a less polar by-product. These fractions are condensed and purified again by column chromatography using 6:1 (v/v) hexane:ethyl acetate and then 2:1 (v/v) hexane:ethyl acetate as developing solvents. The NMR spectrum (CDCl_3) shows singlets at δ 1.33 (6 H, CH_3), 3.12 (2 H, CH_2), 4.12 (broad, OH) and complex signals between 7.24-8.01 (5 H).

3. Discussion

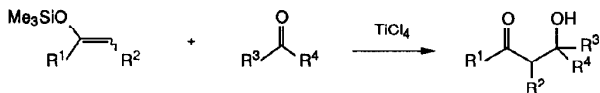
This procedure illustrates a general method for the preparation of crossed aldols. The aldol reaction between various silyl enol ethers and carbonyl compounds proceeds smoothly according to the same procedure (see Table I). Silyl enol ethers react with aldehydes at -78°C , and with ketones near 0°C .³ Note that the aldol reaction of silyl enol ethers with ketones affords good yields of crossed aldols which are generally difficult to prepare using lithium or boron enolates. Lewis acids such as tin tetrachloride and boron trifluoride etherate also promote the reaction; however, titanium tetrachloride is generally the most effective catalyst.

Ketene alkyl silyl acetals may also be used as nucleophiles for the formation of β -hydroxy esters.⁴ The present reaction can be carried out equally well on large or small (mmole) scales. For small scale applications,

it is convenient to prepare a stock solution of titanium tetrachloride in methylene chloride. (A rubber stopper is gradually destroyed by titanium tetrachloride; therefore, a Teflon stopper should be used.) Titanium tetrachloride also promotes the aldol-type reaction between silyl enol ethers and acetals to give β -alkoxy carbonyl compounds.⁵

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Table I. Preparation of Crossed Aldols



Substituents

R ¹	R ²	R ³	R ⁴	Yield of Aldols, %
-(CH ₂) ₄ -		Me ₂ CH	H	92
		PhCH ₂	PhCH ₂	64
-(CH ₂) ₃ -		PhCH ₂	H	95
Ph	H	Me ₂ CH	H	94
Ph	Me	Me	H	92
Ph	Me	PhCO	H	83
Ph	Me	Me	(CH ₂) ₂ CO ₂ Me	53

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Hydroxy-3-methyl-1-phenyl-1-butanone: 1-Butanone, 3-hydroxy-3-methyl-1-phenyl- (9); (43108-74-3)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

Acetone (8); 2-Propanone (9); (67-64-1)

1-Phenyl-1-trimethylsiloxyethylene: Silane, trimethyl[(1-phenylvinyl)oxy]- (8); Silane, trimethyl[(1-phenylethenyl)oxy]- (9); (13735-81-4)

Acetophenone (8); Ethanone, 1-phenyl- (9); (98-86-2)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

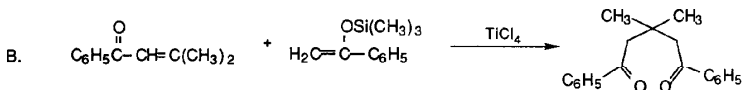
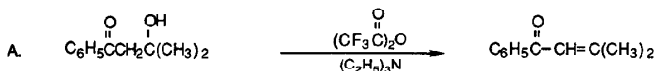
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Sodium iodide (8,9); (7681-82-5)

Acetonitrile (8,9); (75-05-8)

3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE

(1,5-Pentanedione, 3,3-dimethyl-1,5-diphenyl-)



Submitted by Koichi Narasaka.¹

Checked by David E. Uehling and Clayton H. Heathcock.

1. Procedure

A. *Isopropylideneacetophenone*. A 1-L, three-necked flask is fitted with a 100-mL pressure-equalizing dropping funnel, a mechanical stirrer and a condenser which is equipped with a two-way stopcock leading to a balloon of argon gas. To the flask is added a solution of 18.4 g of 3-hydroxy-3-methyl-1-phenyl-1-butanone (Note 1) in 60 mL of dry methylene chloride. The flask is cooled in an ice bath and 28.5 g of triethylamine, a catalytic amount of 4-(N,N-dimethylamino)pyridine and 20 mL of methylene chloride are added. A solution of 25.8 g of trifluoroacetic anhydride (Note 2) in 40 mL of methylene chloride is added dropwise over a period of 15 min, and the mixture is stirred for 2.5 hr.

The ice bath is removed and the mixture is stirred for 21 hr at room temperature (about 30°C). Under vigorous stirring, 100 mL of saturated aqueous sodium carbonate, 100 mL of water and 300 mL of ether are added to the mixture. The organic layer is separated and the water layer is extracted with 100 mL of ether. The combined ether extracts are washed with brine and dried over magnesium sulfate. The ether solution is condensed using a rotary evaporator and the residue is distilled under reduced pressure to give 14.5-16.0 g (88-97% yield) of isopropylideneacetophenone (Note 3).

B. *3,3-Dimethyl-1,5-diphenylpentane-1,5-dione*. A 500-mL, three-necked flask is fitted with a mechanical stirrer, rubber septum and a two-way stopcock which is equipped with a balloon of argon gas (Note 4). To the flask is added 100 mL of dry methylene chloride, and the flask is cooled in a dry ice-acetone bath. Titanium tetrachloride (7.7 mL) (Note 5) is added by syringe through the septum. The septum is removed and replaced with a 100-mL pressure-equalizing dropping funnel containing a solution of 11.2 g of isopropylideneacetophenone in 30 mL of methylene chloride. This solution is added over a 3-min period, and the mixture is stirred for 4 min. A solution of 13.5 g of the silyl enol ether of acetophenone (Note 1) in 40 mL of methylene chloride is added dropwise with vigorous stirring over a 4-min period, and the mixture is stirred for 7 min. The reaction mixture is poured into a solution of 22 g of sodium carbonate in 160 mL of water with vigorous magnetic stirring (Note 6). The resulting white precipitate is removed by filtration through a Celite pad and the precipitate is washed with methylene chloride.

The organic layer of the filtrate is separated and the aqueous layer is extracted with two 40-mL portions of methylene chloride. The combined organic extracts are washed with 60 mL of brine and dried over sodium sulfate.

The methylene chloride solution is concentrated with a rotary evaporator and the residue is passed through a short column of silica gel (Baker 200 mesh, 400 ml) using 1.5 L of a 9:1 (v/v) mixture of hexane and ethyl acetate (Note 7). The eluent is condensed and distilled; the first fraction (bp 81-85°C/0.6 mm, 2.04 g) is a mixture of isopropylideneacetophenone and acetophenone; the second fraction (bp 85-172°C/0.6 mm, 0.42 g) is a mixture of the above substances and the desired product; the third fraction (bp 172-178°C/0.6 mm) gives 14.0-15.2 g (72-78%) of 3,3-dimethyl-1,5-diphenylpentane-1,5-dione (Note 8).

2. Notes

1. See *Organic Syntheses*, this volume p. 6.
2. Attempted dehydration using an acid catalyst or iodine failed, giving mainly acetophenone. When acetic anhydride is employed instead of trifluoroacetic anhydride, the reaction proceeds very slowly. Dehydration with excess methanesulfonyl chloride and triethylamine gives the product in high yield; however, the distilled product has a strong odor of sulfur compound.
3. The physical properties are as follows: bp 73-75°C/0.4 mm; the NMR spectrum (CCl_4) shows singlets at δ 1.93 (3 H) and 2.13 (3 H) and multiplets at 6.63 (1 H), 7.16-7.48 (3 H) and 7.71-7.91 (2 H).
4. All the apparatus should be well dried before use.
5. Freshly distilled titanium tetrachloride (bp 136.4°C) is used.
6. Stirring should be continued until the organic and aqueous layers show no acidity.

7. The submitters used Wako gel C-200.

8. The physical properties are as follows: Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.34; H, 7.16. The 1H NMR spectrum ($CDCl_3$) shows singlets at δ 1.22 (6 H, \underline{CH}_3) and 3.26 (4 H, \underline{CH}_2), and multiplet signals between 7.17-8.03 (10 H, aromatic \underline{CH}).

3. Discussion

The preparation of 3,3-dimethyl-1,5-diphenylpentane-1,5-dione has also been achieved from 3,3-dimethylglutaric acid and phenyllithium.²

The present method gives 3,3-dimethyl-1,5-diphenylpentane-1,5-dione in better yield, and is widely applicable to the preparation of various 1,5-diketones.³ In addition, when silyl enol ethers of esters are employed instead of those of ketones, δ -keto esters can be obtained.⁴

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,3-Dimethyl-1,5-diphenylpentane-1,5-dione: 1,5-Pentanedione,

3,3-dimethyl-1,5-diphenyl- (9); (42052-44-8)

Isopropylideneacetophenone: 2-Buten-1-one, 3-methyl-1-phenyl- (9);

(5650-07-7)

3-Hydroxy-3-methyl-1-phenyl-1-butanone: 1-Butanone,

3-hydroxy-3-methyl-1-phenyl- (9); (43108-74-3)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

4-(N,N-Dimethylamino)pyridine: Pyridine, 4-(dimethylamino)- (8);

4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

Trifluoroacetic anhydride: Acetic acid, trifluoro-

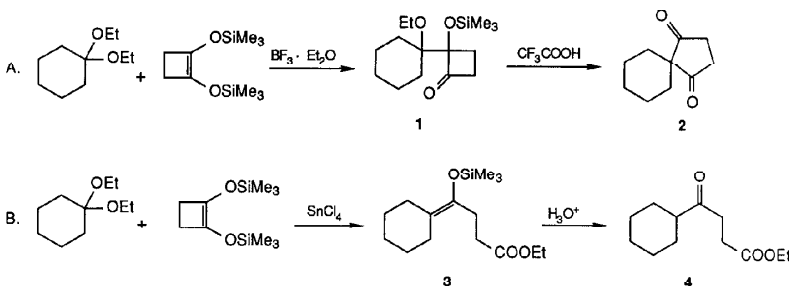
anhydride (8,9); (407-25-0)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

Acetophenone silyl enol ether: Silane, trimethyl[(1-phenylvinyl)oxy]- (8);

Silane, trimethyl[(1-phenylethenyl)oxy]- (9); (13735-81-4)

RING EXPANSION AND CLEAVAGE OF SUCCINOIN DERIVATIVES:
SPIRO[4.5]DECANE-1,4-DIONE AND ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE
(Cyclohexanecarboxylic acid, γ -oxo-, ethyl ester)



Submitted by Eiichi Nakamura and Isao Kuwajima.¹

Checked by Jens Wolff and Ian Fleming.

1. Procedure

A. *Spiro[4.5]decane-1,4-dione* (2). In a dry, 200-mL, two-necked flask with one neck connected to a nitrogen source to maintain a positive pressure and with the other covered with a rubber septum is placed a magnetic stirring bar. Boron trifluoride etherate (5.04 mL, 40.0 mmol) (Note 1) and 40 mL of dry methylene chloride (Note 2) are introduced with a hypodermic syringe and the solution is cooled to ca. -75°C with a dry ice/hexane bath. A mixture of cyclohexanone diethyl ketal (6.88 g, 40 mmol) (Note 3) and 1,2-bis(trimethylsilyloxy)cyclobut-1-ene (9.20 g, 40 mmol) (Note 4) in 20 mL of dry methylene chloride is added during 10 min. The resulting yellow solution is stirred for

30 min at that temperature and 8 mL of trifluoroacetic acid (Note 5) is added. The mixture is warmed to room temperature and stirred for 2 hr (Note 6) before addition of 40 mL of water. The mixture is extracted three times with 100 mL-portions of ether, and the combined extract is washed successively with a 30-mL portion of water, saturated aqueous sodium bicarbonate (2 x 45 mL), and 30 mL of saturated sodium chloride. The extract is dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator at aspirator pressure. The crude, viscous oily material is distilled at 0.05 mm with a Kugelrohr apparatus (Note 7) with an oven temperature at 75-80°C to obtain 5.40-6.00 g (81-90%) of spiro[4.5]decane-1,4-dione, which crystallizes on cooling to room temperature, mp 61-62°C (Note 8).

B. *Ethyl 4-cyclohexyl-4-oxobutanoate* (4). In a dry, 100-mL, two-necked flask with one neck connected to a nitrogen source to maintain a positive pressure and with the other covered with a rubber septum is placed a magnetic stirring bar. Tin tetrachloride (7.50 g, 28.8 mmol) (Note 9) and 15 mL of dry methylene chloride (Note 2) are introduced with a hypodermic syringe and the solution is cooled to ca. -75°C with a dry ice/hexane bath. A mixture of cyclohexanone diethyl ketal (4.82 g, 28.0 mmol) (Note 3) and 1,2-bis(tri-methylsilyloxy)cyclobut-1-ene (6.44 g, 28.0 mmol) (Note 4) in 10 mL of methylene chloride is added during 10 min. The yellow solution is stirred for 15 min at -75°C, and for 15 min at -30°C, during which period the solution turns heterogeneous (Note 10). Water (20 mL) and ether (50 mL) are added and the organic layer is separated. The aqueous layer is extracted twice with ether (50 mL) and the combined organic layers are washed successively with 3 x 10-mL portions of 1 N hydrochloric acid, and 20-mL portions each of water, aqueous sodium bicarbonate, and saturated sodium chloride. The oily product (6.30 g) obtained after drying (anhydrous magnesium sulfate) and concentration

on a rotary evaporator is distilled to give an analytically pure keto ester (4) (5.27-5.44 g, 90-93%) as a fraction boiling at 110-112°C, 2.5 mm, or 84°C, 0.2 mm (Note 11).

2. Notes

1. Boron trifluoride etherate (Hashimoto Kasei Chemical, Osaka) was distilled before use.

2. Methylene chloride was distilled from phosphorus oxide and stored over molecular sieves.

3. Cyclohexanone diethyl ketal was prepared according to a procedure by Howard and Lorette; see *Org. Synth., Collect. Vol. V* **1973**, 292; bp 80-83°C, 18 mm. The checkers prepared it by keeping cyclohexanone (50 g), triethyl orthoformate (75 g) and concentrated hydrochloric acid (0.2 mL) in absolute ethanol (30 mL) for 10 hr at room temperature, followed by treatment with sodium hydroxide until the solution is basic.

4. 1,2-Bis(trimethylsilyloxy)cyclobut-1-ene was prepared in ca. 80% yield on a 0.5-mol scale by Method 2 described by Bloomfield and Nelke; see *Org. Synth.* **1977**, 57, 1.

5. Commercially available trifluoroacetic acid (Tokyo Kasei Co.) was used as received.

6. If trifluoroacetic acid treatment is omitted, the aldol-type adduct, 2-(1-ethoxycyclohexyl)-2-(trimethylsilyloxy)cyclobutanone (1), is obtained in high (ca. 90%) yield; bp 85-90°C (bath temp), 0.05 mm; IR (neat) cm^{-1} : 1789 (s, C=O); ^1H NMR (CCl_4) δ : 0.11 (s, 9 H), 0.9-2.2 (m, including t, $J = 7$ at δ 1.10), 2.2-2.9 (m, 3 H), 3.2-3.7 (AB part of ABX_3 , 2 H). Treatment of purified 1 with trifluoroacetic acid gives 2 in nearly quantitative yield.

7. Kugelrohr distillation ovens are manufactured by Büchi Glasapparatefabrik.

8. The checkers found variable amounts (0-15%) of the ester (4) in the product. This could easily be removed by recrystallization of the diketone from light petroleum (bp 40-60°C) to give needles, mp 62-64°C. The product has the following spectral properties: IR (CCl_4) cm^{-1} : 1720 (vs); ^1H NMR (CCl_4) δ : 1.58 (br s, 10 H), 2.65 (s, 4 H); MS (70 eV) m/e (relative intensity) 166.0983 (M^+ , 100, calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$; 166.0994), 137 (24), 124 (36), 112 (87), 111 (83), 109 (27), 85 (38), 81 (48), 67 (95), 56 (48), 54 (45), 53 (42), 41 (58), 30 (64).

9. Tin tetrachloride (Yoneyama Yakuhin Co.) was distilled before use.

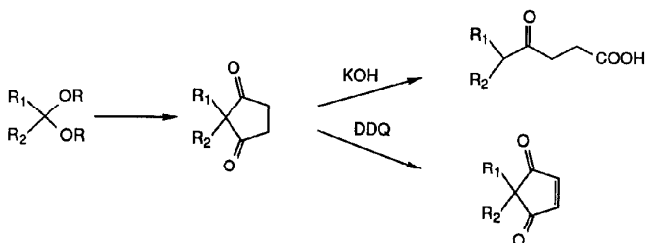
10. If the mixture is quenched with triethylamine before aqueous workup, the intermediate enol silyl ether 3 is obtained; bp 110-115°C (bath temp), 0.04 mm; IR (neat) cm^{-1} : 1745 (s), 1680 (m); ^1H NMR (CCl_4) δ : 0.12 (s, 9 H), 1.3-2.6 (m, 14 H, including t, $J = 7$, at 1.26 and s at 2.36), 4.10 (q, $J = 7$). Addition of aldehydes, acetals, or phenylsulfonyl chloride at this stage gives the respective aldol and sulfonylated products.

11. The product has the following spectral properties: IR (CCl_4), cm^{-1} . 1739 (s), 1713 (s); ^1H NMR (CCl_4) δ : 0.8-1.9 (m, 18 H, including t, $J = 1.28$, CH_2CH_3), 4.15 (q, $J = 7$, OCH_2CH_3); MS (70 eV) m/e (relative intensity) 212 (M^+ , 5), 167 (20), 129 (55), 111 (28), 101 (80), 83 (100), 55 (72), 41 (37), 29 (34).

3. Discussion

The present reactions are based on the novel rearrangement of succinoin derivatives such as 1 which are obtainable in high yield by the reaction of

1,2-bis(trimethylsilyloxy)cyclobut-1-ene with carbonyl compounds. The first procedure, Part A, illustrates a general method for preparing a wide range of spiro[4.n]alkane-1,4-diones as well as useful 2-mono- and 2,2-disubstituted cyclopentane-1,3-diones (Table I).² The combination of an aldol reaction³ and a skeletal rearrangement provides a highly efficient new approach to these synthetically interesting molecules.⁴ The reaction can be performed either in a single pot or as a two-stage operation by isolating the initial aldol adduct 1. The merit of the sequence as a spiro annelation method is illustrated by the synthesis of a 5,8-methanospiro[4.5]decanedione from norcamphor (Table I). γ -Keto acids and cyclopent-2-ene-1,4-diones also become available from ketals in a few steps.



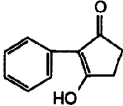
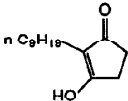
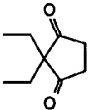
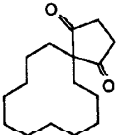

The second procedure, Part B, illustrates an easy synthesis of γ -keto esters by "reductive succinylation" of a ketal function.⁵ It is useful not only for the preparation of keto esters, but also as a four-carbon chain-elongation reaction starting from ketones. The reaction is applicable to a diverse range of ketals as shown in Table II. The enol silyl ether intermediate **3** can either be isolated or used in situ for further elaboration. Fluoride⁶ and Lewis-acid catalyzed aldol reactions cleanly give aldol adducts,⁶ and the reaction with phenylsulfonyl chloride gives α phenylthio ketones in high yield.⁵



Cyclobutanone **1** is also useful for the stereoselective construction of quaternary carbon centers⁷ and 2,3-substituted cyclopentenones.⁸ The synthetic utility of the chemistry of **1** and related compounds has been reviewed.^{7,9}

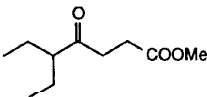
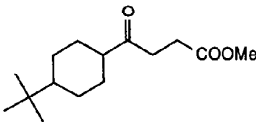
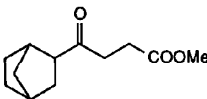
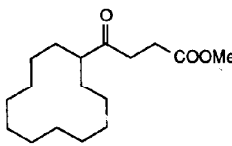
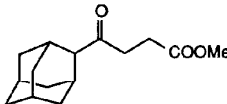
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Table I. Synthesis of Cyclopentane-1,3-diones

Acetal or Ketal	Product	Yield (aldol x rearrangement) ^a
benzaldehyde diethyl acetal		94 x 97%
decanal dimethyl acetal		90 x 87%
3-pentanone dimethyl ketal		92 x 87%
cyclododecanone dimethyl ketal		92 x 94% (91%) ^b
2-norbornanone dimethyl acetal		60 x 92%

^aThe results in this table were obtained by the two stage procedure (i.e. the isolation of the initial adduct, e.g., 1, is involved). ^bYield from the single-pot procedure as described in the text.

Table II. Reductive Succinylation

Ketal	Product	Yield
3-pentanone dimethyl ketal		87
4-tert-butylcyclohexanone dimethyl ketal		92
2-norbornanone dimethyl ketal		90
cyclododecanone dimethyl ketal		91
adamantanone dimethyl ketal		68

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Spiro[4.5]decane-1,4-dione (9); (39984-92-4)

Ethyl 4-cyclohexyl-4-oxobutanoate: Cyclohexanebutanoic acid, γ -oxo-, ethyl ester (9); (54966-52-8)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF_3) (1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

Cyclohexanone diethyl ketal (8); Cyclohexane, 1,1-diethoxy- (9); (1670-47-9)

1,2-Bis(trimethylsilyloxy)cyclobut-1-ene: Silane, (1-cyclobuten-1,2-ylenedioxy)bis[trimethyl- (8); Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl- (10); (17082-61-0)

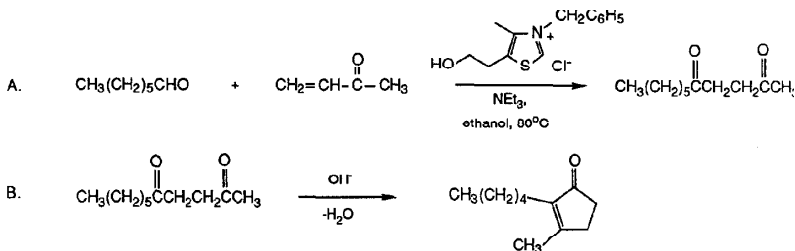
Trifluoroacetic acid. Acetic acid, trifluoro- (8,9); (76-05-1)

Tin tetrachloride: Tin chloride (8); Stannane, tetrachloro- (9); (7646-78-8)

THE STETTER REACTION:

3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE (DIHYDROJASMONE)

(2-Cyclopenten-1-one, 3-methyl-2-pentyl-)



Submitted by H. Stetter, H. Kuhlmann and W. Haese.¹

Checked by Rodney A. Badger and James D. White.

1. Procedure

A. *2,5-Indecanedione*. A 1000-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer, short gas inlet tube, and an efficient reflux condenser fitted with a potassium hydroxide drying tube is charged with 26.8 g (0.1 mol) of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (Note 1), 500 mL of absolute ethanol, 77.2 g (1.1 mol) of 3-buten-2-one (Note 2), 60.6 g (0.6 mol) of triethylamine (Note 3), and 114.2 g (1.0 mol) of heptanal (Note 4). A slow stream of nitrogen (Note 5) is started and the mixture is stirred and heated in an oil bath at 80°C . After 16 hr the reaction mixture is cooled to room temperature and concentrated by rotary evaporation. Then 500 ml of chloroform is added to the residue and the

mixture is washed with 200 mL of dilute hydrochloric acid (5%), 200 mL of saturated sodium hydrogen carbonate solution and, finally, with two 200-mL portions of water. After the solution is dried with anhydrous magnesium sulfate, the chloroform is distilled off and the residue is fractionated under reduced pressure through a 30-cm Vigreux column. The main fraction is collected at 80-82°C/0.3 mm. The yield is 130-138 g (71-75% based on heptanal) of a colorless distillate, which solidifies on standing at room temperature, mp 33-34°C (Note 6, 7).

B. *3-Methyl-2-pentyl-2-cyclopenten-1-one* (*Dihydrojaomono*). 2,5-

Undecanedione (92.1 g, 0.5 mol) is added to a solution of 16.0 g (0.4 mol) of sodium hydroxide in 800 mL of water and 200 mL of ethanol in a 2000-mL round-bottomed flask. The mixture is refluxed for 6 hr, cooled to room temperature, and extracted with ether. The combined ether phases are dried with magnesium sulfate, and the solution is separated from the drying agent and concentrated at room temperature under reduced pressure. The residual oil is distilled through a 30-cm Vigreux column. The pure compound boils at 65-67°C/0.5 mm and weighs 70-73 g (84-88% based on the diketone) (Note 8).

2. Notes

1. 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride is supplied by Fluka AG, Buchs, Switzerland and by Tridom Chemical, Inc., Hauppague, New York. The thiazolium salt may also be prepared as described in *Org. Synth.* 1984, 62, 170.

2. 3-Buten-2-one was used as obtained from Fluka AG, Buchs, Switzerland.

3. Triethylamine was dried with potassium hydroxide and distilled. Instead of triethylamine, sodium acetate (32.8 g, 0.4 mol), which has been dried under vacuum at 100°C for 1 day, can also be used.

4. Heptanal was supplied by Aldrich Chemical Company, Inc. It was freshly distilled before use.

5. The nitrogen flow rate should be one bubble per second.

6. A boiling point of 141°C/14 mm and a melting point of 33°C is recorded.² The diketone exhibits the following spectral characteristics: IR (CDCl₃) cm^{-1} : 1710; ¹H NMR (CDCl₃) δ : 0.77-1.67 (m, 11 H, CH_2 and CH_3); 2.13 (s, 3 H, C- CH_3); 2.30-2.60 (m, 2 H, CH_2); 2.67 (s, 4 H, $\text{COCH}_2\text{CH}_2\text{CO}$).

7. The checkers obtained a second fraction from the distillation (13.5 g, 7.4%), bp 97-105°C/0.15 mm, which solidified upon cooling. Recrystallization of this material from hexane gave a colorless solid, mp 26-27°C, which was identified from its infrared, NMR, and mass spectra as 8-hydroxy-7-tetradecanone. This product arises via a "benzoin-type" condensation, catalyzed by the thiazolium salt, of heptanal.

8. A boiling point of 122-124°C/12 mm is recorded.² The cyclopentenone exhibits the following spectral characteristics: IR (neat) cm^{-1} : 1695 and 1640; ¹H NMR (CDCl₃) δ : 0.77-1.50 (m, 9 H, CH_2 and CH_3); 2.03 (s, 3 H, CH_3); 2.13-2.57 (m, 6 H, CH_2). For fragrance it is advisable to destroy malodorous by-products by the method described in Note 9.

9. The use of sodium acetate instead of triethylamine (see Note 3) is an alternative and is followed by an oxidizing treatment of the diketone: 100 g of 2,5-undecanedione is dissolved in 500 mL of methylene chloride and treated with 10 g of an oxidizing reagent (Note 10). The mixture is refluxed for 3 hr, filtered and washed with three 100-mL portions of water. The organic phase is dried with sodium sulfate and distilled. This material is converted into dihydrojasnone by procedure B, and a last, efficient distillation (Fisher, slit tube-system, HMS 500) leads to chromatographic purity greater than 99 per cent.

10. Oxidizing reagent:³ To a solution of 500 g (0.5 mol) of chromium (VI) oxide and 300 mL of water is added 250 g of silica gel (silica gel 60, E. Merck, Darmstadt, West Germany). The mixture is shaken at 30-35°C for 1 hr. After this, the water is removed on a rotary evaporator to yield a yellow-orange, free-flowing powder.

3. Discussion

2,5-Undecanedione and the cyclization to dihydrojasnone were first described by H. Hunsdiecker.² The natural jasmine odor components and the artificial substitutes have been the goal of many investigations.⁴ Our method of preparing 2,5-undecanedione by addition of heptanal to 3-buten-2-one⁵ is only one example of a wide range of reactions involving the conjugate addition to electron-deficient double bonds.⁶

A large variety of aldehydes has been used in the addition to butenone (we give some characteristic examples):

1. Simple straight-chain aliphatic aldehydes (C_2 to C_{12} tested) and mono α -branched aldehydes.⁷

2. Conjugated unsaturated aldehydes (e.g., citral, β,β -dimethyl-acrolein⁸).

3. Aldehydes that contain isolated double bonds, such as 10-undecenal, citronellal, 3-cyclohexene-1-carboxaldehyde and norbornene carboxaldehyde.^{8,9}

4. Aldehydes containing a variety of other functional groups, e.g., ether groups,¹⁰ the phthalimido group,¹¹ keto, ester and nitrile groups.^{12,13}

5. Heterocyclic and aromatic aldehydes^{7,12} (e.g., furan-2-carboxaldehyde, thiophen-2-carboxaldehyde, the pyridine carboxaldehydes, benzaldehyde, and diverse substituted benzaldehydes).

Variations have been made in the activated system also. Higher homologues of butenone (e.g., 1-penten-3-one, tert-butyl vinyl ketone) react in the same manner, as does phenyl vinyl ketone. The same variety of functional groups as shown before may be possible in the side chain of the ketone.¹⁴

Additions to acrylic esters and acrylonitrile¹⁵ and to arylidene and alkylidene- β -dicarbonyl compounds¹⁶ are possible.

The addition of aldehydes to α,β -unsaturated sulfones yields γ -diketones.¹⁷

The mechanism of the thiazolium ion-catalyzed conjugate addition reactions⁶ is considered to be analogous to the Lapworth mechanism for the cyanide-catalyzed benzoin condensation, the thiazolium ylide playing the role of cyanide. The resulting intermediate carbanion is presumed to be the actual Michael donor. After conjugate addition to the activated olefin, the thiazolium ylide is eliminated to form the product and regenerate the catalyst.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Methyl-2-pentyl-2-cyclopenten-1-one: 2-Cyclopenten-1-one, 3-methyl-2-pentyl- (8,9); (1128-08-1)

2,5-Undecanedione (8,9); (7018-92-0)

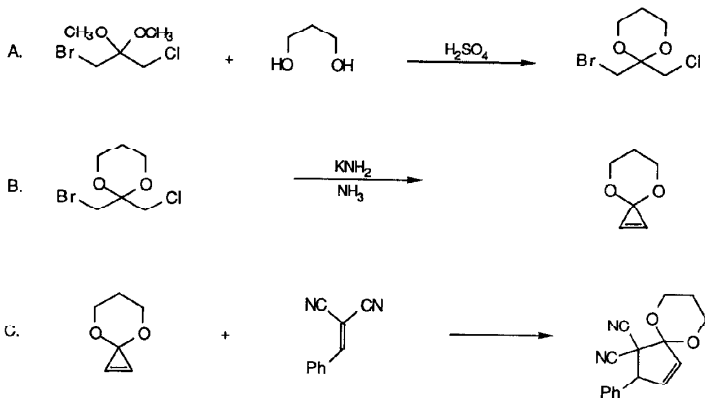
3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (8,9); (4568-71-2)

3-Buten-2-one (8,9); (78-94-4)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

Heptanal (8,9); (111-71-7)

PREPARATION AND THREE-CARBON + TWO-CARBON CYCLOADDITION OF A
CYCLOPROPENONE KETAL: CYCLOPROPENONE 1,3-PROPANEDIOL KETAL
(4,8-Dioxaspiro[2.5]oct-1-ene)



Submitted by Dale L. Boger, Christine F. Brotherton, and Gunda I. Georg.¹

Checked by Steven K. Davidsen and Clayton H. Heathcock.

1. Procedure

A. *2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane*.² A 100-mL, round-bottomed flask is equipped with a 10-mL Dean-Stark apparatus and a condenser. The flask is charged with 30.0 g (0.138 mol) of 1-bromo-3-chloro-2,2-dimethoxypropane (Note 1), 10.0 mL (0.138 mol) of 1,3-propanediol (Note 2), and 3 drops of concentrated sulfuric acid. The resulting solution is heated (bath temperature 140°C) for 8 hr (Note 3) with distillative removal of methanol (ca. 11 mL). The mixture is allowed to cool to room temperature and the crude product is partitioned in 150 mL of pentane and 40 mL of water. The

organic phase is dried with magnesium sulfate and the solvent is removed under reduced pressure (Note 4). Distillation (1 mm, 90-95°C) yields 25.5-27.7 g (81-88%) of 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane. mp 57-59°C (Note 5).

B. *Cyclopropanone 1,3-propanediol ketal*.³ A 1000-mL, three-necked, round-bottomed flask is equipped with a gas inlet, an acetone-dry ice condenser with a drying tube containing potassium hydroxide pellets, a stopper and a magnetic stirring bar. The flask is placed in an acetone-dry ice bath and anhydrous ammonia (Note 6) is condensed into the flask (400 mL). A small piece of potassium metal (ca. 0.5 g) is added to the liquid ammonia and the cooling bath is removed. A catalytic amount of anhydrous ferric chloride (0.1 g) is added and the reaction mixture is allowed to warm to reflux temperature, at which time the deep blue color turns to gray. The remaining potassium metal (12.2 g, 0.31 g-atom total) is added in 0.5-g pieces over ca. 30 min. The reaction mixture is allowed to stir until a gray suspension results (20-30 min). A -50°C cooling bath is placed under the flask and the stopper is replaced with a 125-mL, pressure-equalized dropping funnel containing 22.9 g (0.1 mol) of 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane in 50 mL of anhydrous ether. This solution is added dropwise to the solution of freshly generated potassium amide over 15 min while the temperature is maintained at -50°C (Note 7). After the solution is stirred for 3 hr at -50°C to -60°C, solid ammonium chloride is added slowly to quench the excess potassium amide (Note 8). The cooling bath is removed and the ammonia is allowed to evaporate. During the course of the evaporation, anhydrous ether (350 mL total) is added dropwise through the addition funnel to replace the ammonia. After the temperature has reached 0°C, the brown reaction mixture is filtered by suction through a coarse fritted glass filter to remove the inorganic salts and the calts are washed twice with 25 mL of anhydrous ether. The combined

ethereal filtrate and washes are concentrated under reduced pressure (80-100 mm, 30°C) to a constant weight (ca. 4-5 hr) (Note 9). The residue is transferred to a 50-mL, round-bottomed flask fitted with a water-cooled, short-path distillation head, and the product is distilled (1.25 mm; 30-35°C) into an ice-cooled receiver. Cyclopropanone 1,3-propanediol ketal is obtained as a colorless liquid (6.1-7.8 g, 55-70% yield, Note 10).

C. *5,5-Dicyano-4-phenylcyclopent-2-enone 1,3-propanediol ketal*. Benzylidenemalononitrile (Note 2) (3.85 g, 25 mmol) and cyclopropanone 1,3-propanediol ketal (5.6 g, 50 mmol) are combined in 25 mL of dry distilled toluene (Note 11) in a sealed tube (Note 12) with a magnetic stirring bar. The reaction mixture is heated at 80°C for 6.5 hr with stirring. The crude reaction mixture is filtered through a short plug of glass wool and applied to a Waters Associates Prep LC/System 500, eluting with 2.5:1 hexane/ethyl acetate (Note 13). The fractions containing product are combined and concentrated under reduced pressure to give 4.4-4.2 g (60-64%) of *5,5-dicyano-4-phenylcyclopent-2-enone 1,3-propanediol ketal* as a white solid: mp 139-141°C (ethanol, Note 14).

2. Notes

1. The preparation⁴ of this material has been described in detail: Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth.* 1977, 57, 41.
2. The submitters employed material available from Aldrich Chemical Company, Inc. without further purification.
3. Shorter reaction times result in incomplete transketalization.

4. The checkers found that the product crystallizes, either upon removal of solvent, or in the condenser during the following distillation. To prevent the condenser tube becoming plugged by the crystalline product, an air-cooled, rather than a water-cooled condenser jacket should be used.

5. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 1.70 (m, 2 H, CH_2), 3.70 (s, 2 H, CH_2Cl), 3.00 (s, 2 H, CH_2Br), 3.96 (t, 4 H, $J = 6$, OCH_2); IR (CHCl_3) cm^{-1} : 3030, 3000, 2900, 1485, 1430, 1245, 1202, 1158, 1135, 1105 (s), 1020.

6. Commercial anhydrous ammonia is employed without further drying.

7. Crystals which may form at the tip of the addition funnel are scraped off and allowed to drop into the reaction flask.

8. The checkers added a total of 25 g of solid ammonium chloride in portions of approximately 2 g with a spatula.

9. The checkers removed the solvent with a rotary evaporator at 20 mm and 25°C : under these conditions only 1 hr is required to concentrate the solution to a constant weight.

10. This material should be stored under an argon atmosphere below 0°C . The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 1.83 (m, 2 H, CH_2), 4.01 (t, 4 H, $J = 6$, OCH_2), 7.84 (s, 2 H, $\text{CH}=\text{CH}$); ^{13}C NMR (CDCl_3) δ : 25.4 (CH_2), 65.6 (OCH_2), 80.5 (OCO), 125.1 ($\text{C}=\text{C}$); IR (film) cm^{-1} : 3101, 2980, 2870, 1600, 1475, 1460, 1435, 1370, 1300, 1275, 1155, 1090, 1030, 935, 910, 865, 740.

11. Toluene was distilled from calcium hydride under a nitrogen atmosphere.

12. The resealable glass tube was fabricated from an Ace Glass medium-walled straight tube. The tube was permanently sealed on one end and the other end remained internally threaded. The tube was sealed with a solid Teflon plug fitted with a FETFE O-ring. Various sizes of such tubes are now available from Ace Glass.

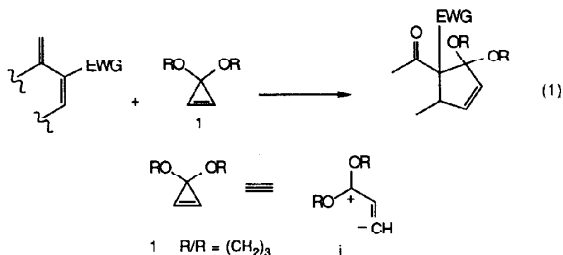
13. The submitters used medium pressure chromatography⁵ on 25 x 1000 mm of 230-400 mesh silica gel with a 25 x 250 mm scrubber column. The eluant (3:1:1 hexane:ethyl acetate:methylene chloride) was passed through the column at a rate of 15 mL/min, collecting 15 mL fractions. The checkers were unable to obtain pure product using a gravity column or flash chromatography.

14. The product has the following spectral properties: ¹H NMR (CDCl₃) δ: 1.71 (dt, 1 H, J = 13.8, J = 3.8, OCH₂CH₂CH₂O), 2.1-2.3 (broad m, 1 H, OCH₂CH₂CH₂O), 3.9-4.3 (m, 4 H, OCH₂CH₂CH₂O), 4.63 (t, 1 H, J = 2.3, allylic CH), 6.25 (dd, 1 H, J = 6.3, J = 2.0, CH-CH=CH-C), 6.62 (dd, 1 H, J = 6.3, J = 2.6, CH-CH=CH-C), 7.3-7.5 (m, 5 H, phenyl); IR (CHCl₃) cm⁻¹: 3070, 2920, 2290 (C≡N), 1510, 1465, 1350, 1260, 1210, 1175, 1140, 1100, 1080, 1040, 870, 705.

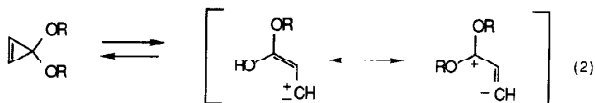
3. Discussion

Although a number of multistep procedures are available for the introduction of five-membered carbocycles, their direct formation in a thermal cycloaddition is rare.⁶ Interest in the potential application of such a three-carbon + two-carbon cyclopentane cycloaddition has been derived from the expectation that such a process could prove to be an effective complement to the four-carbon + two-carbon Diels-Alder reaction which is used extensively in the regio- and stereocontrolled preparation of functionalized six-membered carbocycles.

Cyclopropanone ketals, of which cyclopropanone 1,3-propanediol ketal (1) is a representative and unusually stable example, have proven to be useful equivalents of the 1,3-dipole (i) in a regiospecific three-carbon + two-carbon cycloaddition with electron-deficient olefins, (eq 1). Table I shows representative results of a study of this reaction.⁷

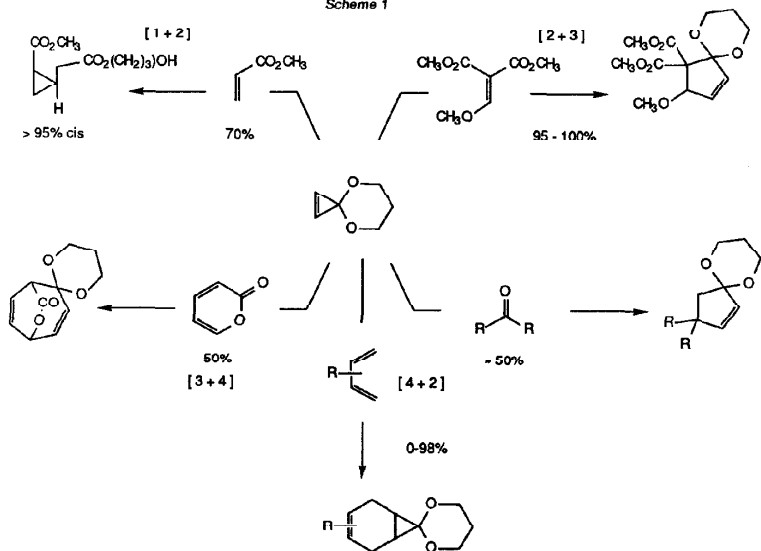


Studies have defined the scope of the thermal reactions of cyclopropanone ketals which are characterized by their thermal, reversible ring opening to provide reactive intermediates best represented as delocalized singlet vinyl carbenes, three-carbon 1,1-/1,3-dipoles without octet stabilization, (eq 2).



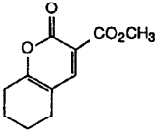
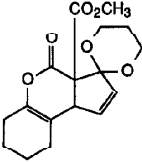
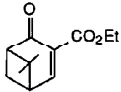
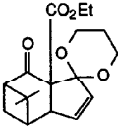
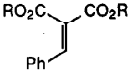
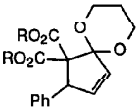
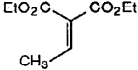
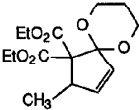
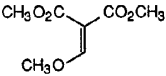
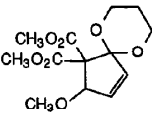

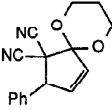
In addition to the representative [3 + 2] cycloaddition reactions shown in Table I, the delocalized singlet vinyl carbenes have been shown to participate as $\pi 2_a$ components of non-linear cheletropic [$\pi 2_s + \pi 2_a$] cycloadditions to provide cyclopropanes with an observable endo effect,⁸ and as $\pi 2_s$ components of [$\pi 4_s + \pi 2_s$] cycloadditions with selected dienes to provide cycloheptadienes,⁹ (Scheme 1). This thermal reactivity of cyclopropanone ketals

Scheme 1



complements their dual participation as strained olefins in normal ($\text{HOMO}_{\text{diene}}$ controlled) and inverse electron demand ($\text{LUMO}_{\text{diene}}$ controlled) Diels-Alder reactions with electron-rich, electron-deficient, and neutral dienes under room temperature, thermal, and pressure-promoted Diels-Alder conditions.¹⁰

Table I. Reactions of Cyclopropenone Ketal 1 with Electron-deficient Olefins

Substrate	Conditions ^a	Product	%Yield
equiv 1, temp. °C(time hr)			
	1.0-2.0,80(12)		42%
	1.0,75(13)		45%
	1.5,75(10) 2.5,75(32)		48% 60%
	1.5,75(15)		57%
	2.0,80(5)		84%
	2.0,80(4)		60-64%

(a) All reactions were run in benzene (0.5 - 2.0 M in substrate) under nitrogen unless otherwise noted.

1. Department of Medicinal Chemistry, The University of Kansas, Lawrence, KS 66045. Present address: Department of Chemistry, Purdue University, West Lafayette, IN 47907.
2. Butler, G. B.; Herring, K. H.; Lewis, P. L.; Sharpe, V. V., III; Veazey, R. L. *J. Org. Chem.* **1977**, *42*, 679.
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8. Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611.
9. Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclopropanone 1,3-propanediol ketal: 4,8-Dioxaspiro[2.5]oct-1-ene (9);
(60935-21-9)

2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane: 1,3-Dioxane, 2-(bromomethyl)-
2-(chloromethyl)- (9); (60935-30-0)

1-Bromo-3-chloro-2,2-dimethoxypropane: 2-Propanone, 1-bromo-3-chloro-,
dimethyl acetal (8); Propane, 1-bromo-3-chloro-2,2-dimethoxy- (9);
(22089-54-9)

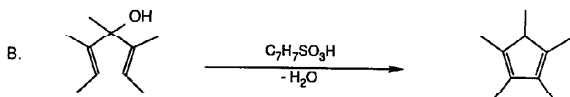
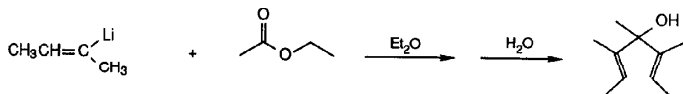
1,3-Propanediol (8,9); (504-63-2)

5,5-Dicyano-4-phenylcyclopent-2-enone 1,3-propanediol ketal:
6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl- (11);
(88442-12-0)

Benzylidenemalononitrile: Malononitrile, benzylidene- (8); Propanedinitrile,
(phenylmethylene)- (9): (2700-22-3)

1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE

(1,3-Cyclopentadiene, 1,2,3,4,5-pentamethyl-)



Submitted by Richard S. Threlkel,¹ John E. Bercaw,¹ Paul F. Seidler,²
Jeffrey M. Stryker,² and Robert G. Bergman.²

Checked by David E. Hill and James D. White.

1. Procedure

A. *3,4,5-Trimethyl-2,5-heptadien-4-ol*. Lithium wire (1/8") is cut up into approximately 1-cm lengths and washed with hexane (Note 1). A mixture of the cut-up lithium (21 g, 3.0 mol) in 100 mL of diethyl ether from a freshly opened can is stirred well under argon in a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser and a 250-mL addition funnel. 2-Bromo-2-butene (cis and trans mixture) is purified and dried by passing it through a 2 x 15-cm column of basic alumina I (Note 2). An addition funnel is charged with 2-bromo-2-butene (200 g, 1.48 mol) and a small amount of the alkene is added dropwise to the flask until reaction begins, as shown by warming of the

reaction mixture and formation of bubbles on the surface of the lithium (Note 3). At this point the mixture is diluted with an additional 900 mL of fresh diethyl ether, and the remainder of the 2-bromo-2-butene is added at a rate sufficient to maintain gentle reflux. Stirring is continued for 1 hr following completion of this addition, after which ethyl acetate (66 g, 0.75 mol) diluted with an equal volume of fresh diethyl ether is added dropwise via the addition funnel. The reaction mixture turns from yellow-orange to milky-yellow with this addition. It is then poured into 2 L of saturated aqueous ammonium chloride. The ethereal layer is separated, and the aqueous layer is adjusted to approximately pH 9 with hydrochloric acid. The aqueous layer is extracted three times with diethyl ether. The combined ethereal layers are dried over magnesium sulfate, filtered, and concentrated to 100-200 mL by rotary evaporation.

B. 1,2,3,4,5-Pentamethylcyclopentadiene. A mixture of 13 g (0.068 mol) of p-toluenesulfonic acid monohydrate and 300 mL of diethyl ether is stirred under argon in a 1-L, three-necked, round-bottomed flask equipped with a reflux condenser and a 250-mL addition funnel. The concentrate from above is added as quickly as possible to the flask from the addition funnel, maintaining a gentle reflux. As the reaction proceeds, a water layer separates. The mixture is stirred for 1 hr after the addition is completed and then washed with saturated aqueous sodium bicarbonate until the washings remain basic. The ethereal layer is separated, and the combined aqueous layers are extracted three times with diethyl ether. The combined ethereal layers are dried over sodium sulfate. Diethyl ether is removed by rotary evaporation, and the crude product is distilled under reduced pressure (bp 55-60°C, 13 mm): yield 73-75 g (73-75%) (Note 4).

2. Notes

1. High sodium lithium (1-2% sodium) is preferred in order to facilitate initiation of the reaction. (The checkers used 1% sodium in lithium wire purchased from Lithium Corporation of America, Bessemer City, NC).

2. While published procedures have used samples of 2-bromo-2-butene as obtained from the supplier without further purification, impurities in some batches often make it difficult, if not impossible, to start the reaction safely.

3. *Caution! It is imperative to add only a few mL of the 2-bromo-2-butene and to patiently wait for the reaction with the lithium to begin. Addition of too much 2-bromo-2-butene too soon may lead to a violent reaction.*

4. Pentamethylcyclopentadiene has the following spectral properties; IR (neat) cm^{-1} : 2940, 2890, 2840, 2730, 1670, 1655, 1440, 1370; ^1H NMR (CDCl_3) δ : 1.00 (3 H, d, $J = 7.6$, CH_3CH), 1.8 (12 H, br s, $\text{CH}_3\text{C}-$), 2.45 (1 H, q, $J = 6.5$, CHCH_3).

3. Discussion

The procedure described here is a modification of that previously published.³ Specifically, it is frequently insufficient to use the 2-bromo-2-butene as obtained from the supplier without purification using basic alumina I. Such purification assures facile reaction with lithium. Furthermore, the large volumes of diethyl ether used in the past are unnecessary and may inhibit initiation of the reaction of 2-bromo-2-butene with lithium. Finally, while dry solvents and reagents are required, diethyl ether from a freshly opened can is sufficiently free of water, and distillation from lithium aluminum hydride is unnecessary.

1,2,3,4,5-Pentamethylcyclopentadiene is a useful aromatic building block for the preparation of other compounds. It can be converted to many salts of its conjugate base with alkali metals or strong bases such as butyllithium.⁴ These pentamethylcyclopentadienyl anion salts as well as the diene itself can be transformed into η^5 -pentamethylcyclopentadienyl ligands of organotransition metal complexes by many known methods.⁴

1. Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125.
2. Department of Chemistry, University of California, Berkeley, CA 94720.
3. Threlkel, R. S.; Bercaw, J. E. *J. Organomet. Chem.* **1977**, *136*, 1.
4. Feitler, D.; Whitesides, G. M. *Inorg. Chem.* **1976**, *15*, 466; Green, M. L. H.; Pardy, R. B. A. *J. Chem. Soc., Dalton Trans.* **1979**, 355 and references therein.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,2,3,4,5-Pentamethylcyclopentadiene: 1,3-Cyclopentadiene, 1,2,3,4,5-pentamethyl- (9); (4045-44-7)

3,4,5-Trimethyl-2,5-heptadien-4-ol: 2,5-Heptadien-4-ol, 3,4,5-trimethyl- (9); (64417-15-8)

Lithium (8,9); (7439-93-2)

Diethyl ether: Ethyl ether (8); Ethane, 1,1'-oxybis- (9); (60-29-7)

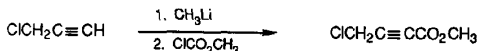
2-Bromo-2-butene (cis and trans mixture): 2-Butene, 2-bromo- (9); (13294-71-8)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

ALKOXYCARBONYLATION OF PROPARGYL CHLORIDE:

METHYL 4-CHLORO-2-BUTYNOATE

(2-Butynoic acid, 4-chloro-, methyl ester)



Submitted by M. Olomucki and J. Y. Le Gall.¹

Checked by H. T. M. Le and M. F. Semmelhack.

1. Procedure

Caution! Propargyl chloride, methyl chloroformate and methyl 4-chloro-2-butynoate are vesicants and lachrymators. This preparation should be conducted in a ventilated hood and protective gloves should be worn.

A 250-mL, round-bottomed flask is equipped with stirring bar (Note 1), thermometer, and a pressure-equalizing dropping funnel (dried in an oven at 80°C, assembled while still hot) and the system is placed under argon (Note 2). Via syringe, 7.45 g (7.16 mL, 0.1 mol) of propargyl chloride (Note 3) and 35 mL of anhydrous diethyl ether (Note 4) are added. The solution is stirred and cooled to -50°C to -60°C (Note 5) with an alcohol-dry ice bath (Note 6). Under gentle argon pressure, 72.4 mL of 1.41 M solution of methyllithium in diethyl ether (Note 7) is added dropwise over ca. 20 min (Note 8). Stirring is continued for 15 min and 18.9 g (0.2 mol) (Note 9) of methyl chloroformate (Note 10) is added through the dropping funnel over ca. 10 min. The reaction mixture is allowed to warm slowly (3-4 hr) to 0°C to -5°C during which time a fine precipitate appears. Water (40 mL) is added dropwise with efficient

stirring; the ether layer is separated and the aqueous layer is extracted two times with ether. The combined ether solutions are dried over anhydrous magnesium sulfate, and the ether is removed under reduced pressure with a rotary evaporator. The residual liquid is distilled in a simple distillation assembly under reduced pressure, affording 10.7-11.1 g (81-83%) of methyl 4-chloro-2-butyrate as a colorless liquid, bp 41°C (0.25 mm), n_D^{22} 1.4728 (Note 11).

2. Notes

1. The submitters specify a mechanical stirrer; the checkers find magnetic stirring to be more convenient and equally effective.

2. The system was alternately evacuated with an oil pump and then filled with argon three or more times, and a positive pressure was maintained throughout the reaction period. The submitters used nitrogen in place of argon.

3. Propargyl chloride (98% purity), obtained from Fluka AG, was used without further purification.

4. Ether was dried over sodium wire.

5. Although cooling to -20 to -30°C is sufficient, the addition of methyllithium is more convenient at lower temperatures.

6. The checkers used a constant temperature refrigerated bath (Cryocool).

7. Methyllithium in the form of solutions in diethyl ether is supplied by Aldrich Chemical Company, Inc. in rubber septum stoppered bottles, which should be stored in a refrigerator.

8. The solution of methyllithium was conveniently handled using techniques for the manipulation of air-sensitive reagents.²

9. Lower yields were obtained when less methyl chloroformate was used. Thus, the yield was about 55% when the reaction was performed with one equivalent of methyl chloroformate, and 70-72% with 1.5 mol of the latter per mol of propargyl chloride.

10. Methyl chloroformate was used as supplied by Fluka AG (98% purity).

11. The product gives satisfactory elemental analysis and shows the following IR spectrum (film) cm^{-1} : 2267, 1725, 720.

3. Discussion

Methyl 4-chloro-2-butyrate has been prepared³ in 54% yield by treatment of 4-chloro-2-butyric acid with 10% sulfuric acid in methanol. 4-Chloro-2-butyric (chlorotetrollic) acid has been prepared³ in 40% yield by chromic acid oxidation of 4-chloro-2-butyne-1-ol (the latter obtained⁴ in 45% yield by the reaction of 2-butyne-1,4-diol with thionyl chloride) or in 85% yield by treatment of the lithium derivative of propargyl chloride with carbon dioxide.⁵

The present synthesis illustrates a convenient preparation of chlorotetrollic esters which can be performed in one step starting from commercially available and inexpensive products; it is faster and gives better yields as compared with the overall yields of the multistep preparations described earlier. Since chlorotetrollic acid is not an intermediate in this synthesis, the necessity of distilling this explosive product is eliminated. In contrast to the acid, explosions were never observed during distillations of the lower boiling chlorotetrollic esters.

Other 4-chloro-2-butynoic esters can be obtained by varying the alkyl chloroformates. Thus, ethyl 4-chloro-2-butynoate was prepared⁶ in the same way in 60% yield, and tert-butyl 4-chloro-2-butynoate in 73% yield; the procedure could probably be further generalized. When butyllithium is used in these syntheses instead of methylolithium, much lower (ca. 30%) yields are obtained.

Chlorotetrolic esters are small, highly functionalized, reactive molecules; of particular interest is the possibility of using them as reagents for chemical modification of biological macromolecules. Different protein nucleophiles react under mild conditions with methyl 4-chloro-2-butynoate by addition across the triple bond and/or substitution of chlorine⁷ while the triple bond and the ester group are involved in the reaction of chlorotetrolic esters with nucleic acid bases.⁸

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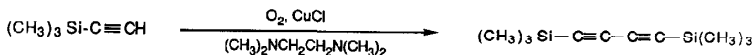
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- Propargyl chloride: Propyne, 3-chloro- (8); 1-Propyne, 3-chloro- (9);
(624-65-7)
- Methyl 4-chloro-2-butyrate: 2-Butyric acid, 4-chloro-, methyl ester (9);
(41658-12-2)
- Methyl chloroformate: Formic acid, chloro-, methyl ester (8);
- Carbonochloridic acid, methyl ester (9); (79-22-1)
- Methyl lithium: Lithium, methyl- (8,9); (917-54-4)

1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE
(Silane, 1,3-butadiyne-1,4-diylbis[trimethyl-])



Submitted by Graham E. Jones, David A. Kendrick, and Andrew B. Holmes.¹

Checked by James Armstrong and Clayton H. Heathcock.

1. Procedure

A. Copper(I) chloride - tetramethylethylenediamine complex. A 200-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, nitrogen inlet tube, and bubbler is charged with acetone (90 mL) and copper(I) chloride (5 g, 51 mmol) (Note 1). After the flask is purged with nitrogen, the mixture is stirred and N,N,N',N'-tetramethylethylenediamine (TMEDA) (2.5 mL, 16.6 mmol) (Note 2) is added. Stirring is maintained for 30 min, and the solid material is then allowed to settle, leaving a clear deep blue-green solution of the CuCl-TMEDA catalyst which is used in the oxidative coupling reaction.

B. 1,4-Bis(trimethylsilyl)buta-1,3-diyne (BTMSHD). A 1-L, four-necked flask, equipped with a mechanical stirrer (Note 3), dry ice cold-finger condenser (Note 4), sintered gas inlet, and a swan-neck adapter which supports a thermometer and rubber septum is charged with acetone (300 mL) and trimethylsilylacetylene (50 g, 0.51 mmol) (Note 5). The reaction mixture is agitated and a rapid stream of oxygen is passed through the solution (Note 6). The supernatant solution containing the CuCl-TMEDA catalyst is:

transferred by syringe in 5-mL portions into the reaction vessel. The temperature rises as the catalyst is added and should have reached 35°C after about 75% of the catalyst has been added. When this temperature is reached, external ice cooling is applied to moderate the exothermic reaction (Note 7). The remaining catalyst is added and the temperature is maintained in the range of 25-30°C for 2.5 hr (Note 8). When the reaction is complete there should be no evidence of trimethylsilylacetylene condensing on the cold trap. Agitation and oxygenation are then stopped.

The acetone is removed by evaporation with a rotary evaporator, and the residue is dissolved in petroleum ether (bp 30-40°C, 150 mL) (Note 9) and shaken in a separatory funnel with 3 M aqueous hydrochloric acid (150 mL). The phases are separated and the aqueous phase is washed with petroleum ether (bp 30-40°C, 3 x 150 mL). The combined organic layers are washed with saturated aqueous sodium chloride (50 mL), dried (Na_2SO_4), and evaporated to dryness with a rotary evaporator. The solid residue is dissolved in hot methanol (400 mL) to which has been added 3 M aqueous hydrochloric acid (4 mL). The solution may be filtered at this stage if it is necessary to remove colored insoluble impurities. Water is then added dropwise until recrystallized material is permanently present. The solution is allowed to cool, finally in ice, and crystalline bis(trimethylsilyl)butadiyne (BTMSBD) is collected. The material is washed with a small portion of ice-cold methanol-water (50:50 v/v; 50 mL), and dried in the air to give bis(trimethylsilyl)butadiyne (31-35 g, 68-76%), mp 111-112°C (lit.^{2,3} 107-108°C) (Note 10). A further 3-5 g (6-10%) of the product is obtained from the mother liquors (Notes 11 and 12).

2. Notes

1. Copper(I) chloride, S.L.R. grade, was used as supplied by Fisons Scientific Apparatus Ltd. Best results are obtained with fresh samples of copper(I) chloride which usually contains $\leq 2\%$ copper(II) chloride. Further purification⁴ did not improve the yield of BTMSBD. The checkers used Mallinckrodt Chemical Company, Analytical Reagent Grade copper(I) chloride, without further purification.

2. N,N,N',N'-Tetramethylethylenediamine (TMEDA) (98%) was used as supplied by B.D.H. The checkers used 99% TMEDA, as supplied by Aldrich Chemical Company, Inc.

3. Mechanical stirring is adequate for a 50-g scale, as described herein, and magnetic stirring is sufficient for a 5-g scale. The submitters ran the procedure on a 200-g scale, and found that use of a Vibro-mixer is essential to obtain satisfactory oxygenation of the reaction mixture. The Vibro-mixer model E-1 was supplied by Chemap AG, Alte Landstr. 415, CH-8708, Mannedorf, Switzerland.

4. The reactant is sufficiently volatile in the fast oxygen stream that substantial loss of material occurs unless a cold finger condenser with a large contact area, charged with dry ice-2-propanol, is used. The use of a short Vigreux column between the dry ice condenser and the reaction vessel is strongly recommended to provide additional protection against loss of material as an aerosol.

5. Trimethylsilylacetylene is prepared by silylation of ethynylmagnesium chloride as described in the accompanying procedure in Organic Syntheses. It is also commercially available from the Aldrich Chemical Company, Inc.

6. *CAUTION.* Although no hazard has been encountered in this reaction, due care should be taken with acetylenic compounds in an atmosphere of oxygen. The experiment should be conducted in a well-ventilated hood behind a safety shield and away from any source of ignition. Dilution of exit gases (T-joint) with nitrogen is strongly advised.

7. On two occasions the temperature was observed to reach 35°C well before 75% of the catalyst had been added by the checkers. The temperature should be monitored closely during this addition. If ice cooling is necessary, it is important to lower the temperature only to 25°C; otherwise the reaction will become too sluggish. After the internal temperature is brought to 25°C, further cooling is not needed during addition of the remaining catalyst.

8. A deep blue-green coloration should be evident throughout the addition of the catalyst. The color is determined by the rate of oxygen flow. Too high a flow rate can lead to over-oxidation, producing a black precipitate, whereas too low a flow rate can lead to over-reduction of the catalyst, with the green color fading to be replaced by an orange-red precipitate. Both factors reduce the yield of BTMSBD.

9. The checkers used pentane instead of petroleum ether.

10. The checkers observed mp 109-110°C for all crops.

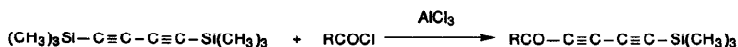
11. Yields of 95% on a 5-g scale, and 70-75% on a 200 g scale were reproducibly obtained by the submitters.

12. Pure bis(trimethylsilyl)butadiyne exhibits the following spectroscopic data: IR (CCl_4) cm^{-1} : 2080 (s), 1250 (s), and 650 (s); UV (C_6H_{12}) nm max(ϵ): 224 (80), 235 (150), 248 (260), 262 (345), and 278 (250); ^1H NMR (CDCl_3 , 250 MHz) δ : 0.22 (18 H).

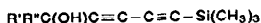
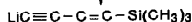
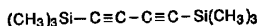
3. Discussion

Oxidative coupling of terminal acetylenes in the presence of copper(I) catalysts is the best method of preparing symmetrically substituted butadiyne derivatives,⁵ and has been applied to the coupling of trimethylsilylacetylene.⁶ Better yields are obtained using the Hay procedure in which the catalyst is the TMEDA complex of copper(I) chloride.⁷ The procedure submitted here is an improved version of Walton and Waugh's synthesis of BTMSBD by the Hay coupling of trimethylsilylacetylene.² BTMSBD has also been prepared by silylation of butadiynedimagnesium bromide³ and chloride⁸ in moderate yield, and more recently from the dilithium derivative in good yield.²⁵

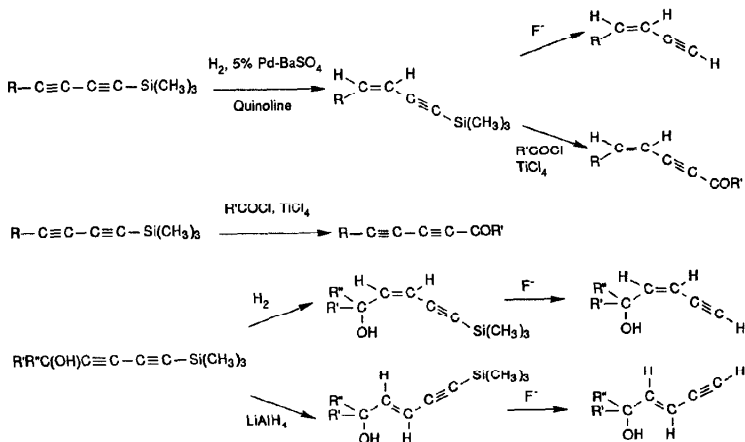
BTMSBD is a very convenient source of butadiyne, an extremely useful, but dangerously explosive chemical.⁹ It is also a synthon for the vinylacetylene anion. A single trimethylsilyl group can selectively be replaced by reaction with electrophiles (Friedel-Crafts reaction) to give trimethylsilylbutadiynyl ketones.²



Alternatively, a more nucleophilic anionic reagent can be generated by selective cleavage of a single trimethylsilyl group with methyllithium-lithium bromide complex.¹⁰ This lithiobutadiyne derivative will react with electrophiles such as carbonyl compounds^{10,11} or primary alkyl iodides.¹²



Regio- and stereoselective reduction of the non-silylated triple bond, either by partial catalytic hydrogenation,^{13,14,15} or by lithium aluminum hydride reduction of the propargylic alcohols,^{11,16,17} afford (after desilylation), respectively, terminal (Z)- and (E)-enynes. Furthermore, the remaining trimethylsilyl group in both silylated diynes and enynes may be replaced by another electrophile in a second Friedel-Crafts reaction.¹⁸



Such reactions have found a variety of applications in natural products synthesis.^{11,13,14,16,17,19}

BTMSBD reacts with a variety of nucleophiles to give novel heterocycles such as selenophen,²⁰ tellurophen,²¹ and pyrazoles.²² It has also been used in [2+4] cycloaddition/cycloreversion sequences to prepare ethynyl-substituted pyridazines²³ and furans.²⁴

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,4-Bis(trimethylsilyl)buta-1,3-diyne: 2,7-Disilaocta-3,5-diyne,
2,2,7,7-tetramethyl- (8); Silane, 1,3-butadiyne-1,4-diylbis[trimethyl- (9);
(4526-07-2)

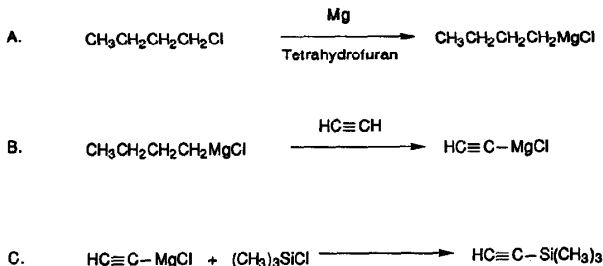
Copper(I) chloride: Copper chloride (8,9); (7758-89-6)

N,N,N',N'-Tetramethylenediamine: Ethylenediamine, N,N,N',N'-tetramethyl- (8);

1,2-Ethanediamine, N,N,N',N'-tetramethyl- (9); (110-18-9)

Trimethylsilylacetylene: Silane, ethynyltrimethyl- (8,9); (1066-54-2)

TRIMETHYLSILYLACETYLENE
(Silane, ethynyltrimethyl-)



Submitted by Andrew B. Holmes and Chris N. Sporikou.¹

Checked by Dallas D. Crotts, Bruce E. Eaton, and Clayton H. Heathcock.

1. Procedure

A. *Butylmagnesium chloride.* A dry, 1-L, three-necked, round-bottomed flask is equipped with a sealed mechanical stirrer (Note 1), a 250-mL pressure-equalizing dropping funnel, and a reflux condenser to the top of which is attached a T-piece connected at one end to a supply of dry nitrogen, and at the other to an oil or mercury bubbler. At the same time a dry, 2-L, three-necked, round-bottomed flask, fitted with a sealed mechanical stirrer and two swan neck adapters, is prepared, with one adapter holding a gas inlet and a calcium chloride drying tube, and the other supporting a thermometer and a 1-L pressure-equalizing dropping funnel.

The 1-L flask is charged with magnesium turnings (39.6 g, 1.65 g-atom) (Note 2) and dry tetrahydrofuran (THF) (150 mL), the mixture is heated to reflux temperature under an atmosphere of dry nitrogen, and a crystal of iodine is added. The dropping funnel is filled with 1-chlorobutane (173 mL, 152.5 g, 1.65 mol) (Note 3) and a portion (15 mL) is added to the boiling THF mixture. The source of heat is removed. After the reaction has commenced, the THF begins to boil more vigorously and a further volume (400 mL) of THF is added to the reaction mixture. Then the remainder of the chlorobutane is added slowly at a rate sufficient to maintain the reaction under reflux. Finally, the reaction mixture is stirred and heated under reflux until all the magnesium has been consumed (0.5-1 hr).

B. *Ethyneylmagnesium chloride*. While the butylmagnesium chloride is being prepared, the 2-L flask is filled with dry THF (500 mL), which is saturated by bubbling acetylene through it for 0.5-1 hr (Note 4). The warm (ca. 60°C) butylmagnesium chloride is rapidly poured under a liberal blanket of nitrogen into the 1-L dropping funnel which is then flushed with nitrogen before being stoppered. The rapid flow of acetylene is maintained. The 2-L flask is cooled to -5°C in a dry ice-acetone bath, the acetylene is bubbled rapidly through the THF (Note 4), and the butylmagnesium chloride is added dropwise to the stirred reaction mixture at a rate sufficient to maintain the temperature below 20°C (Note 5). This addition requires 1 hr; then acetylene is bubbled through the reaction mixture for a further 0.5 hr (the mixture cools to about 5°C during this period). The acetylene supply is disconnected and replaced by dry nitrogen.

C. *Trimethylsilylacetylene*. A solution of chlorotrimethylsilane (152 mL, 130 g, 1.197 mol) (Note 6) in dry THF (100 mL) is placed in the 1-L dropping funnel and is added (20 min) to the cooled and stirred solution of

ethynylmagnesium chloride at a rate sufficient to maintain a reaction temperature of about 15-20°C (Note 7). Finally, the dropping funnel is replaced by an efficient double surface condenser and calcium chloride drying tube, and the reaction mixture is heated under reflux for 1 hr (Note 8). The reflux condenser is replaced by a distillation head and a double surface condenser is connected to a receiver flask which is cooled in an ice bath (Note 9). The reaction mixture is distilled under nitrogen with stirring until all the azeotrope of trimethylsilylacetylene and THF (700-800 mL, bp ca. 66°C) has distilled (Notes 10, 11). The distillate is washed with ice-water portions (10 x 500 mL) to remove the THF. Washing is continued until the organic layer stays constant in volume (Note 12). Distillation (Note 10) of the organic layer under an atmosphere of nitrogen through a short Vigreux column (Note 13) gives trimethylsilylacetylene, bp 50-52°C/760 mm, n_D^{20} 1.391 (lit.^{2,3,4} 53.5°C/762 mm, n_D^{21} 1.3900; 52°C/760 mm, n_D^{20} 1.3900; 52°C/760 mm, n_D^{20} 1.3935) in yields ranging from 72.5 g (62%) to 87.5 g (75%) (Notes 14, 15).

2. Notes

1. The checkers used an efficient magnetic stirrer.
2. The magnesium turnings for Grignard reactions were supplied by Fisons Scientific Apparatus, Loughborough. If less than 1.65 g-atom of magnesium is used, the final product will be contaminated with 1-chlorobutane.
3. It is essential that the 1-chlorobutane be free of 1-butanol. 1-Chlorobutane (Aldrich Chemical Company, Inc.) was purified by rapid passage through basic alumina (activity 1) before use.

4. Gaseous acetylene is introduced at the rate of about 20 L/hr and is purified by passage through a cold trap (-78°C), followed by bubbling through concentrated sulfuric acid and finally passage over sodium hydroxide pellets. These operations must be conducted in a well-ventilated fume hood. The checkers found that an insufficient acetylene flow rate in this and the next step results in the formation of butyltrimethylsilane and bis(trimethylsilyl)acetylene.

5. The temperature reaches 15°C after 0.5 hr, and 20°C after 0.8 hr. Ethynylmagnesium halides can rapidly disproportionate to bis(chloromagnesium)-acetylene and acetylene at higher temperatures.² It is important to maintain the reaction mixture at or below 20°C and to have an excess of acetylene in order to prevent formation of the bis(magnesium chloride). The checkers found that the ethynylmagnesium chloride can be formed at 10 - 15°C , thus minimizing the problem.

6. Commercial chlorotrimethylsilane is distilled from quinoline under nitrogen.

7. It is important that the addition be done fairly rapidly. The checkers found that slow addition (2 hr at 20°C) resulted in significant disproportionation of the ethynylmagnesium chloride.

8. It is essential to have an efficient condenser during the reflux and distillation stages because the product, trimethylsilylacetylene, is extremely volatile.

9. The receiver must be cooled to avoid serious loss of volatile product.

10. The hot distillation apparatus should be allowed to cool under a nitrogen atmosphere before being dismantled.

11. The submitters distilled the azeotrope immediately after heating the mixture to reflux. If it is allowed to stand and cool it sets solid with magnesium chloride and subsequent distillation results in appreciably lower yields.

12. The presence of residual THF in the final product is easily detected by the characteristic ^1H NMR signals at δ 1.85 (4 H) and 3.75 (4 H). The checkers found GLC to be more convenient than ^1H NMR for analysis at this point. Either a 6' x 2 mm glass column of 3% OV-101 on WHP 80/100 with 30 mL/min He or a 15 m x 0.25 mm fused silica capillary column of DB-5 (cross-linked phenylsilicone) with 1 mL/min H_2 proved sufficient to resolve butane, trimethylsilylacetylene, butyltrimethylsilane, THF, 1-chlorobutane, and bis(trimethylsilyl)acetylene.

13. The checkers used an 18-inch Vigreux column, equipped with an adjustable reflux ratio take-off. The final product can be contaminated with up to several per cent butane unless careful distillation is carried out.

14. Trimethylsilylacetylene displayed the following spectroscopic properties: IR (CCl_4) cm^{-1} : 3280 (s) and 2050 (s); ^1H NMR: (CDCl_3 , 250 MHz) δ : 0.10 (s, 9 H, CH_3) and 2.36 (s, 1 H, $\equiv\text{CH}$).

15. The submitters have carried out the preparation on twice the above scale with no reduction in yield.

3. Discussion

Trimethylsilylacetylene has been prepared by silylation of a variety of ethynyl metal derivatives.²⁻¹⁰ The most useful methods are the silylation of ethynylmagnesium bromide^{3,4,5} and chloride.^{2,7,10} The use of ethynylmagnesium bromide has been reported to suffer from complicating side reactions,² and the results obtained in our hands were unreliable.

The present method is based on the silylation of ethynylmagnesium chloride as reported by Krüerke,² except that the Grignard reagent is prepared from 1-chlorobutane, rather than from the volatile (and therefore more difficult to manipulate) chloromethane. Although the preparation of ethynylmagnesium bromide is a well established Organic Syntheses procedure,¹¹ the use of ethynylmagnesium chloride has received little attention.⁵ It does not seem to be widely appreciated that butylmagnesium chloride is much more soluble in THF than ethylmagnesium bromide and its use in Grignard ethynylations is strongly recommended. The preparation of ethynylmagnesium chloride essentially follows the Organic Syntheses procedure laid down for the bromide.¹¹

Trimethylsilylacetylene is an extremely versatile (and potentially nucleophilic) two-carbon building block. Applications in organic synthesis have been well documented in the literature.^{12,13,14}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

Trimethylsilylacetylene: Silane, ethynyltrimethyl- (8,9); (1066-54-2)

Magnesium (8,9); (7439-95-4)

Iodine (8,9); (7553-56-2)

1-Chlorobutane: Butane, 1-chloro- (8,9); (109-69-3)

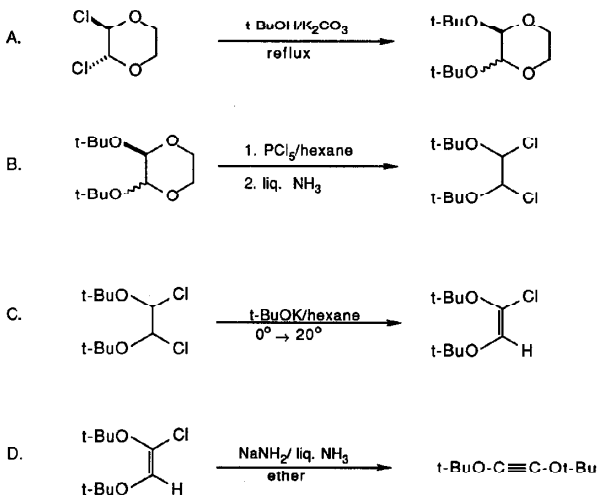
Acetylene (8); Ethyne (9); (74-86-2)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

DIALKOXYACETYLENES: DI-*tert*-BUTOXYETHYNE,

A VALUABLE SYNTHETIC INTERMEDIATE

(Propane, 2,2'-[1,2-ethynediylbis(oxy)]bis[2-methyl-])



Submitted by Anna Bou, Miquel A. Pericàs, Antoni Riera
and Fèlix Serratosa.¹

Checked by Terry Singleton, Jae Chan Park, Martin F. Semmelhack,
Sean M. Kerwin, and Clayton H. Heathcock.

1. Procedure

A. *Preparation of trans-2,3-dichloro-1,4-dioxane* (Note 1). To a 2-L, three-necked, round-bottomed flask, equipped with two inlet tubes (with sintered-glass diffusers at the end) connected to a chlorine cylinder, and a

reflux condenser connected to an outlet tube immersed in a potassium hydroxide solution, are added 1200 g (13.64 mol) of anhydrous dioxane (free of peroxides!) and 8 g (0.03 mol) of iodine. A stream of chlorine is passed through the dioxane/iodine solution heated at 90°C, and the reaction is monitored by NMR spectroscopy. After 9 hr, the conversion is 50% complete (Note 2); after 33 hr, about 90% complete. At this point, the stream of chlorine is interrupted. *Reinitiation of the chlorine stream after some hours (next morning, for example) may be dangerous because it was observed in one case that the mixture inflamed spontaneously!* The reaction mixture is allowed to cool to room temperature, 500 mL of ether is added, and the solution is washed with aqueous sodium thiosulfate solution. The organic layer is separated, dried over sodium sulfate, the ether is evaporated under reduced pressure, and the residue is distilled through a 20-cm Vigreux column, to yield 1200-1300 g of trans-2,3-dichloro-1,4-dioxane, bp 89°C/16 mm (lit.^{2a} bp 82.5°C/14 mm; mp 31°C) (Note 3).

2,3-Di-tert-butoxy-1,4-dioxane. To a 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, reflux condenser protected from moisture by a drying tube, and an inlet tube for dry nitrogen, are added 103.6 g (0.66 mol) of trans-2,3-dichloro-1,4-dioxane, 979.1 g (13.23 mol) of anhydrous tert-butyl alcohol (distilled from CaH₂), and 365.1 g (2.64 mol) of potassium carbonate (ground with a mortar and pestle and activated at 250°C for 3 hr) (Note 4). The mixture is stirred vigorously and heated under reflux for 24-30 hr, the progress of the reaction being monitored by ¹H NMR spectroscopy. Once the singlet at δ 5.95, corresponding to the methine protons of the starting material, has completely disappeared, the reaction mixture is allowed to cool to room temperature, poured into 500 mL of ether, and enough water (750-850 mL) is added to dissolve all of the inorganic

salts. The organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of ether. The combined ether extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 128-147 g of an oily residue (Note 5). Hexane (250 mL) is added and the solution is allowed to stand in a refrigerator. The resulting crystals are separated by suction filtration and washed thoroughly with 150-250 mL of hexane. The residue of 3-6 g of crystalline product, mp 106-107°C, which remains insoluble, is identified as trans-2-tert-butoxy-3-hydroxy-1,4-dioxane (Note 6). The filtrate (which contains approximately a 25:75 mixture of cis and trans isomers) is evaporated under reduced pressure to one-half its volume and is cooled to 0°C. Massive crystals appear which are collected by suction filtration. The crystallization process is repeated once more, to give 40-60 g of trans-2,3-di-tert-butoxy-1,4-dioxane, mp 64-65°C. The hexane solution is evaporated under reduced pressure and the oily residue distilled at 50-57°C/0.25 mm to give 54-84 g of a mixture of cis- and trans-2,3-di-tert-butoxy-1,4-dioxane (115-124 g combined; 75-81% yield) (Note 7).

B. *1,2-Di-tert-butoxy-1,2-dichloroethane*. To a 250-mL, round-bottomed flask, equipped with a pressure-equalizing dropping funnel protected from moisture by a drying-tube, and a magnetic stirring bar, are added 43.2 g (0.21 mol) of phosphorus pentachloride and 50 mL of hexane, and the flask is cooled with an ice-salt bath. While the solution is stirred, a solution of 30 g (0.13 mol) of 2,3-di-tert-butoxy-1,4-dioxane in 100 mL of hexane is added dropwise. After the addition is complete, the cooling bath is removed and the mixture is stirred at room temperature for 90-180 min until no starting material is observed in the NMR spectrum of a sample (Note 8); the reaction mixture is then filtered through a sintered-glass filter to remove excess phosphorus pentachloride. The resulting hexane solution (~ 200 mL), which

contains 1,2-di-tert-butoxy-1,2-dichloroethane, 2-chloroethyl dichlorophosphate, 1,2-dichloroethane, phosphorus oxychloride and traces of phosphorus pentachloride, is transferred into a 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a dry-ice condenser protected from moisture by a potassium hydroxide tube, and a short inlet tube connected to an ammonia cylinder. The reaction flask is cooled with a dry ice/acetone bath and, while the solution is stirred (Note 9), a fast stream of gaseous ammonia is introduced. A vigorous reaction takes place and a copious white precipitate forms. The stream of gaseous ammonia is continued for 15-60 min (Note 10). The cooling bath and condenser are removed, the reaction flask is connected to an ordinary aspirator line through a potassium hydroxide drying trap, and the ammonia is evaporated under aspirator vacuum with efficient stirring. The ammonia-free solution is filtered through a sintered-glass filter and the precipitate is washed with hexane. The resulting hexane solution (400-500 mL), which contains 25-26 g (0.12 mol) of pure 1,2-di-tert-butoxy-1,2-dichloroethane, is suitable for the next operation (yields, calculated from an aliquot, are 95-97%) (Note 11).

C. *(R)-1,2-Di-tert-butoxy-1-chloroethane*. The solution prepared above is placed in a 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a Liebig condenser (protected from moisture by a drying tube) and cooled with an ice bath; 28.9 g (0.258 mol) of solid potassium tert-butoxide is added in small portions through the condenser over a 30-min period. After addition, the cooling bath is removed and stirring is continued for 90-120 min until no more starting material is detected in the ^1H NMR spectrum of a sample; enough ice water is then added to just dissolve all the inorganic salts. The organic layer is separated and the aqueous layer is extracted with hexane (2 x 100 mL). The combined hexane extracts are dried over anhydrous

sodium sulfate, filtered, and concentrated at aspirator vacuum. The residue is distilled at 40°C/0.2 mm, with the collection flask at -78°C, to give a center cut of (E)-1,2-di-tert-butoxy-1-chloroethene (15.4-17.0 g, 58-63% yield from 2,3-di-tert-butoxy-1,4-dioxane) (Notes 12, 13).

D. *Di-tert-Butoxyethyne*. In a 2-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 14), dry-ice condenser protected from moisture by a potassium hydroxide tube, and a pressure-equalizing dropping funnel, 0.5 mol of sodium amide is prepared in 500 mL of liquid ammonia (Note 15), and 20 g (0.0968 mol) of (E)-1,2-di-tert-butoxy-1-chloroethene dissolved in 150 mL of anhydrous ether is added in a 5-min period with efficient stirring. After the addition, stirring is continued for 80 min. The reaction mixture is diluted with 200 mL of cold pentane (-20°C to -30°C), and 400 mL of cold water is added very cautiously. The organic layer is washed with 50 mL of a 0.1 M buffered phosphate solution ($\text{NaH}_2\text{PO}_4/\text{Na}_2\text{HPO}_4$), dried over anhydrous sodium sulfate (Note 16), filtered and concentrated at aspirator vacuum without heating to give 10-12 g (78-86% yield) of di-tert-butoxyethyne as a pale yellow oil. The product is sufficiently pure for further reactions (Note 17), but it may be distilled at 30°C/0.05 mm; freezing point 8.5°C.

2. Notes

1. This procedure was reported J. J. Kucera and D. C. Carpenter.²

2. These data were obtained by the checkers. The submitters report conversion of 76-80% after only 9 hr. It seems likely that the rate of the reaction may be sensitive to the dimensions and mechanical features of the chlorine introduction system, and/or an induction period. It is easy and important to monitor the process.

3. *trans*-2,3-Dichloro-1,4-dioxane has the following spectra; IR (CCl_4) cm^{-1} : 2990, 2940, 2885, 1455, 1385, 1375, 1337, 1160, 1115, 1032, 900, 875, 670; ^1H NMR (CCl_4)^{2b} δ : 3.40-4.57 (AA'BB', 4 H, CH_2), 5.95 (s, 2 H, ClCHO).

4. The yields of this reaction are very sensitive to the presence of traces of moisture, and to the ratio of reagents. If one works without a nitrogen atmosphere and with *tert*-butyl alcohol which has not been previously dried over calcium hydride, with a 1:10 ratio of dichloro derivative/alcohol, the yields drop to 65%.

5. *Caution should be exercised in evaporation of the ether, as the di-*tert*-butoxy compounds are appreciably volatile at reduced pressure. If a rotary evaporator is used for the concentration, the water bath should be kept at or below room temperature, and the residue should not be pumped after it is clear that the bulk of the ether has been evaporated.* The submitters report ca. 130 g of oily residue at this stage. Treatment of the oily residue with 105 mL of ether leads to partial crystallization. During washing of the crystals in a Büchner filter with more ether, an almost complete solubilization takes place, but eventually 0.1-0.5 g of *cis*-2,3,7,10-tetraoxabicyclo[4.4.0]decane remains as an insoluble residue. This compound was prepared for the first time in 1931;³ the *cis* configuration was only established in 1966.⁴ It has the following properties: mp 136°C; IR (CCl_4) cm^{-1} : 2980, 2955, 2930, 2910, 2875, 1460, 1350, 1285, 1260, 1250, 1150, 1140, 1095, 1080, 1025, 910, 870, 780; ^1H NMR (CCl_4) δ : 3.30-4.20 (AA'BB', 8 H, CH_2), 4.60 (s, 2 H, OCHO).

6. The crystalline *trans* isomer epimerizes in chloroform solution to give a nearly 70:30 mixture of *cis* and *trans* isomers. The *trans* isomer, mp 106-107°C, shows the following spectroscopic properties: IR (KBr) cm^{-1} : 3450, 2980, 2935, 2890, 1445, 1390, 1370, 1335, 1280, 1260, 1200, 1135, 1105,

1060, 1045, 1035, 1020, 910, 855, 780; ^1H NMR (CCl_4) δ : 1.27 (s, 9 H, CH_3), 3.33-4.13 (ABCD + OH, 4 H + 1 H) 4.57 (br, 2 H, OCHO). Anal. Calcd for $\text{C}_8\text{H}_{16}\text{O}_4$: C, 54.53; H, 9.15. Found: C, 54.53; H 9.29.

7. trans-2,3-Di-tert-butoxy-1,4-dioxane has the following spectra: IR (CCl_4) cm^{-1} : 2975, 2930, 1390, 1367, 1190, 1145, 1100, 1060, 1040, 857; ^1H NMR (CCl_4) δ : 1.19 (s, 18 H, CH_3), 3.05-4.20 (m, AA'BB', 4 H, CH_2), 4.30 (s, 2 H, OCHO). cis- + trans-2,3-Di-tert-butoxy-1,4-dioxane have the following additional signals: IR (CCl_4) cm^{-1} : 1170, 1130, 1120, 1080, 1020, 1000, 960, 879; ^1H NMR (CCl_4) δ : 4.43 (s, 2 H, OCHO , cis).

8. The peaks corresponding to 2,3-di-tert-butoxy-1,4-dioxane overlap with those of the methylene protons of 2-chloroethyl dichlorophosphate, a by-product from the reaction, but the absence of the acetal protons of the starting material is clear from the symmetry of the multiplet.

9. The solution is thick at -78°C . Dilution with additional hexane may be necessary.

10. The end of the reaction can be easily detected because, when all of the 2-chloroethyl dichlorophosphate has been destroyed, the reaction mixture *does not crackle* any more when condensed ammonia drops on the stirred mixture, or, much more easily, when the reaction mixture becomes basic to pH paper.

11. The crude reaction mixture is, in fact, an approximately 30:70 mixture of dl- and meso-1,2-di-tert-butoxy-1,2-dichloroethane. Although the ^1H NMR spectrum at 60 MHz (CCl_4) shows only one singlet at 5.6 ppm, the 200 MHz spectrum (CDCl_3) shows two sharp singlets separated by 1.8 Hz. The pure meso compound could be isolated by crystallization and purified by sublimation at $40^\circ\text{C}/0.05$ mm; mp $77-78^\circ$ (dec). The spectra are as follows: IR (CCl_4) cm^{-1} : 2975, 2925, 1470, 1458, 1390, 1368, 1310, 1250, 1180, 1130, 1025, 850, 650; ^1H NMR at 200 MHz (CDCl_3) δ : 1.36 (s, 9 H, CH_3), 5.73 (s, 1 H, OCHCl).

12. In later fractions, small amounts (0.2-0.5%) of (Z)-1,2-di-tert-butoxy-1-chloroethene have been detected: $^1\text{H NMR}$ (CCl_4) δ : 1.25 (s, 9 H CH_3), 1.33 (s, 9 H, CH_3), 6.03 (s, 1 H, $=\text{CH}$).

13. (E)-1,2-Di-tert-butoxy-1-chloroethene has the following properties: n_D^{25} 1.4410-1.4415; UV (cyclohexane): 217.7 nm ($\log \epsilon = 3.7$); IR (CCl_4) cm^{-1} : 2972, 1670, 1470, 1390, 1366, 1290, 1260, 1240, 1180, 1140, 1070, 1025, 935; $^1\text{H NMR}$ (CCl_4) δ : 1.26 (s, 9 H, CH_3), 1.33 (s, 9 H, CH_3), 5.91 (s, 1 H, $=\text{CH}$).

14. The stirring bar must be glass-covered, since sodium in ammonia solution attacks Teflon.

15. The method used for the preparation of sodium amide is a modification of the procedure described by Nieuwland, Vaughn, and Vogt.⁵ In a 3-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 14), a dry-ice condenser protected from moisture by a potassium hydroxide tube, and an inlet tube connected to the ammonia cylinder, is condensed 500 mL of liquid ammonia. A slow stream of dry oxygen is initiated through the inlet tube and 11.5 g (0.5 mol) of sodium in small pieces is slowly introduced. The addition of sodium requires 4-5 hr, since the blue color must be discharged before each new addition of sodium. In this way, a completely white suspension of sodium amide is obtained, which allows the formation of crude di-tert-butoxyethyne, free from any iron impurities.

16. It is best to minimize exposure of di-tert-butoxyethyne to light.

17. Eventually, if a more concentrated solution of (E)-1,2-di-tert-butoxy-1-chloroethene in ether is used, the formation of 1,2,3-tri-tert-butoxy-3-cyano-1-propene [$^1\text{H NMR}$ (CCl_4) δ : 6.05 (s, 1 H), 4.98 (s, 1 H), 1.28 (br, 27 H)] and 1,2,3-tri-tert-butoxy-1-cyano-1-propene [$^1\text{H NMR}$ (CCl_4) δ : 4.03 (s, 2 H), 1.28 (b, 27 H)] is observed. The by-products may be eliminated by

column chromatography on neutral alumina (40 g, 100-125 mesh, activity 1), using a column refrigerated at 0°C and protected from the light, and eluting with pentane under nitrogen pressure. From the first 750 mL of eluant, 9-12 g of pure di-tert-butoxyethyne is obtained.

18. Di-tert-butoxyethyne has the following properties: n_D^{25} 1.4365; IR (CCl₄) cm⁻¹: 2972, 2922, 1470, 1450, 1390, 1367, 1301, 1263, 1245, 1150, 825; ¹H NMR (CCl₄) δ : 1.31 (s, CH₃).

3. Discussion

The present procedure for the preparation of di-tert-butoxyethyne is an improvement of a method previously reported by the submitters,⁶ who have also reported the preparation from glyoxal via 1,2-dichloro-1,2-dimethoxyethane.⁶

Although acetylenic diethers are thermodynamically stable compounds, they show a high kinetic instability that induces polymerization even at low temperatures.⁷

Different acetylenic diethers have been prepared, either from glyoxal (method B) or from dioxane (method A); their stability correlates well, in a qualitative way, with Charton's ν steric parameter,⁸ based on effective Van der Waals radii for the corresponding alkoxy groups:

ACETYLENIC DIETHERS



-OR	Method	ν	$t_{1/2}$ Order of magnitude (by NMR)
-OCH ₃	B ⁹	0.38	seconds (0°C, soln.)
-OC ₂ H ₅	B ⁷	0.48	seconds (0°C, soln.)
-OCH ₂ C(CH ₃) ₃	A ¹⁰	0.70	minutes (r.t., soln.)
-OCH(CH ₃) ₂	A,B ⁶	0.75	minutes (r.t., soln.)
-OC(CH ₃) ₃	A,B ⁶	1.22	days (r.t., neat)

As shown above, di-tert-butoxyethyne is the only acetylenic diether prepared so far whose stability allows its use as a synthetic intermediate. It has been used in the synthesis of all the members of the series of monocyclic oxocarbons (deltic, squaric, croconic, and rhodizonic acids),¹¹ as well as in the synthesis of semisquaric acid, the parent compound of the natural mycotoxins, *moniliformins*.¹²

Di-tert-butoxyethyne, like other acetylenic ethers having hydrogen atoms at the α position, is thermally unstable, and when a benzene solution is heated under reflux, elimination occurs to give isobutene and tert-butoxyketene. tert-Butoxyketene then reacts with the parent acetylene to afford 2,3,4-tri-tert-butoxycyclobutenone, which is the precursor of squaric and semisquaric acid.^{11,12} This thermal instability prevents the use of di-tert-butoxyethyne in those reactions that proceed at temperatures higher than 40-50°C, such as some Diels-Alder condensations.

On the other hand, di-tert-butoxyethyne is prone to undergo a variety of reactions with metal transition complexes $[\text{PdCl}_2 \cdot \text{CH}_3\text{CN}]$, $\text{Co}_2(\text{CO})_8$, $\text{CpCo}(\text{CO})_2$, $\text{Ni}(\text{CO})_4$, to afford new, transient, intermediate complexes which are the actual precursors of oxocarbons.¹³

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- Di-tert-butoxyethyne: Propane, 2,2'-[1,2-ethynediylbis(oxy)]bis[2-methyl- (10); (66478-63-5)
- trans-2,3-Dichloro-1,4-dioxane: p-Dioxane, 2,3-dichloro-, trans- (8); 1,4-Dioxane, 2,3-dichloro-, trans- (9); (3883-43-0)
- Dioxane: p-Dioxane (8); 1,4-Dioxane (9); (123-91-1)
- Chlorine (8,9); (7782-50-5)
- tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)
- trans-2,3-Di-tert-butoxy-1,4-dioxane: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans- (10); (68470-79-1)
- cis-2,3-Di-tert-butoxy-1,4-dioxane: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis- (10); (68470-78-0)
- dl-1,2-Di-tert-butoxy-1,2-dichloroethane: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediyl)]bis(oxy)bis[2-methyl-, (R*,R*)-(±)- (10); (68470-80-4)
- meso-1,2-Di-tert-butoxy-1,2-dichloroethane: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediyl)]bis(oxy)]bis[2-methyl-, (R*,S*)- (10); (68470-81-5)
- Phosphorus pentachloride: Phosphorus chloride (8); Phosphorane, pentachloro- (9); (10026-13-8)
- 2-Chloroethyl dichlorophosphate: Phosphorodichloridic acid, 2-chloroethyl ester (8,9); (1455-05-6)
- 1,2-Dichloroethane: Ethane, 1,2-dichloro- (8,9); (107-06-2)
- Phosphorus oxychloride: Phosphoryl chloride (8,9); (10025-87-3)
- Ammonia (8,9); (7664-41-7)

(E)-1,2-Di-tert-butoxy-1-chloroethene: Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E)- (10); (70525-93-8)

Potassium tert-butoxide: tert-Butyl alcohol, potassium salt (8); 2-Propanol, 2-methyl-, potassium salt (9); (865-47-4)

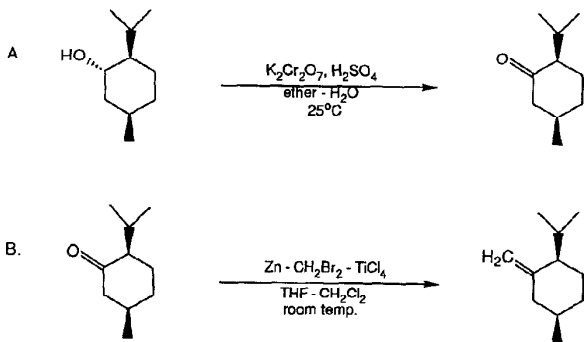
Sodium amide (8,9); (7782-92-5)

Sodium (8,9); (7440-23-5)

cis-2,5,7-10-Tetraoxabicyclo[4.4.0]decane: p-Dioxino[2,3,-b]-p-dioxin, hexahydro- (8); [1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro (9); (4362-05-4)

METHYLENATION OF CARBONYL COMPOUNDS: (+)-3-METHYLENE-*cis*-*p*-MENTHANE

(Cyclohexane, 4-methyl-2-methylene-1-(1-methylethyl)-, *R,R*-)



Submitted by Luciano Lombardo.¹

Checked by Mamoru Uchiyama and Ryoji Noyori.

1. Procedure

A. *(+)-Isomenthone*. Into a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, condenser, thermometer and dropping funnel, are placed 54.6 g (0.35 mol) of *(+)-isomenthol* (Note 1) and 350 mL of ether. A solution of chromic acid, prepared by mixing 56.7 g (0.23 mol) of potassium dichromate and 31.0 mL (0.58 mol) of 98% sulfuric acid and diluting to 200 mL with water, is added dropwise to maintain the reaction temperature at 25°C. The mixture is stirred for a further 2 hr. The ether layer is separated and the aqueous phase is extracted twice with 100-mL portions of ether. The combined ether extracts are washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated under

reduced pressure to leave an oil. Distillation through a short Vigreux column gives the main fraction of (+)-isomenthone as a clear colorless liquid (40.5 g), bp 64-64.5°C/5 mm; $[\alpha]_D^{16} +114^\circ$ [CHCl_3 , c 5.09].

B. (+)-3-Methylene-cis-p-menthane. Into a 1-L, round-bottomed flask fitted with a magnetic stirrer and a pressure equalizing dropping funnel connected to a nitrogen line are placed 28.75 g (0.44 mol) of activated zinc powder (Note 2), 250 mL of dry tetrahydrofuran (Note 3), and 10.1 mL (0.144 mol) of dibromomethane (Note 4). The mixture is stirred and cooled with a dry ice/acetone cooling bath at -40°C. To the stirred mixture is added dropwise 11.5 mL (0.103 mol) of titanium tetrachloride (Note 4) over 15 min. The cooling bath is removed and the mixture is stirred (Note 5) at 5°C (cold room) for 3 days under a nitrogen atmosphere. The dark grey slurry (Note 6) is cooled with an ice/water bath and 50 mL of dry dichloromethane (Note 7) is added. To the stirred mixture is added 15.4 g (0.1 mol) of (+)-isomenthone in 50 mL of dry dichloromethane over a period of 10 min. The cooling bath is removed and the mixture is stirred at room temperature (20°C) for 1.5 hr. The mixture is diluted with 300 mL of pentane and a slurry of 150 g of sodium bicarbonate in 80 mL of water is added cautiously (Note 8) over 1 hr. The clear organic solution is poured off into a 1.5-L Erlenmeyer flask and the residue is washed three times with 50-mL portions of pentane. The combined organic solutions are dried over a mixture of 100 g of sodium sulfate and 20 g of sodium bicarbonate (Note 9), filtered through a sintered glass funnel (No. 2), and the solid desiccant is thoroughly washed with pentane. The solvent is removed at atmospheric pressure by flash distillation through a column (40 cm x 2.5 cm) packed with glass helices. The liquid residue is distilled (Note 10) to give the methylenated product as a clear, colorless liquid, bp 105-107°C/90 mm, 13.6 g, 89% yield (Note 11), n_D^{24} 1.45321, $[\alpha]_D^{23} +/./$ to $+8.6^\circ$ [CHCl_3 , c 4.0].

2. Notes

1. (+)-Isomenthol was purchased from the Aldrich Chemical Company, Inc. Oxidation was carried out according to the procedure of Brown.²
2. Zinc powder from Hopkin and Williams Chemical Company or Nakarai Chemicals (GR grade) is activated according to Fieser and Fieser.³
3. Tetrahydrofuran is dried by distillation from sodium/benzophenone.
4. Dibromomethane from EGA-CHEMIE and titanium tetrachloride from E. Merck are used as supplied. The checkers used the products of Nakarai Chemicals. All residues of titanium tetrachloride are destroyed with acetone from a wash bottle.
5. As the reaction progresses the mixture thickens and it is necessary to begin with a reasonably fast rate of stirring. However, too fast a stirring rate causes the mixture to splash up to the neck of the round-bottomed flask as the mixture thickens.
6. The reagent must be kept cold at all times because at room temperature the active reagent slowly decomposes and the mixture darkens considerably. Once prepared the reagent can be stored at -20°C (freezer) in a well-sealed flask without a significant loss of activity. A sample stored in this way for 1 year showed only a slight, ~ 5-10%, loss of activity. The molar activity of the active reagent is equivalent to the titanium tetrachloride (TiCl_4) molarity (determined by reaction with excess ketone followed by GLC analysis); however, an increase in the proportion of TiCl_4 makes no difference to the molar activity.
7. Analytical Reagent ANALAR dichloromethane was dried by storing over 4Å sieves. The checkers purchased the EP grade solvent from Wako Pure Chemical Industries.

8. It is necessary to add the slurry dropwise at the beginning, allowing the effervescence to subside after each drop. After the initial vigorous effervescence, larger portions can be added. During this part of the addition, the stirrer becomes ineffective and gentle shaking by hand is continued until effervescence ceases.

9. The organic solution is shaken with the drying agent for 10-15 min to remove the last traces of titanium salts.

10. The pressure is allowed to drop to ~ 40 mm for a few minutes when the oil bath temperature has reached 50°C. This procedure removes any residual tetrahydrofuran which can be responsible for a small contaminated forerun. A considerable amount of product is collected at the end of the distillation as the temperature drops.

11. This is the first preparation of this compound (see reference 9 of discussion); the data obtained are as follows: Anal. Calcd for $C_{11}H_{20}$: C, 86.83, H, 13.48. Found: C, 86.76, H, 13.24. 1H NMR ($CDCl_3$, 200 MHz) δ : 0.79 (d, 3 H, $J = 7$, $-CH_3$); 0.91 (d, 6 H, $J = 7$, $-CH_3$); 1.01-2.14 (m, 9 H, $-CH_2-$, $-CH$); 4.54, 4.60, (two s, 2 H, $=CH_2$); ^{13}C NMR ($CDCl_3$): 17.4, 18.3, 19.2, 22.6, 25.8, 26.5, 31.8, 37.3, 47.4, 104.6, 148.4.

3. Discussion.

This new $Zn/CH_2Br_2/TiCl_4$ procedure⁴ provides a mild, non-basic method for the methylenation of ketones (a competitive pinacol dimerization occurs with aldehydes but good yields of the olefin can still be achieved) and offers an important alternative to the standard Wittig⁵ reaction. These characteristics are derived from two important observations:

(i) Ketones are not enolized by the reagent and one important consequence is that adjacent enolizable chiral centers are not epimerized.

(ii) The reagent is compatible with a wide variety of functional groups, for example (Table I), THP ethers, tert-butyldimethylsilyl ethers, acetals, esters, carboxylic acids, alcohols, lactones. Such selectivity makes it a valuable procedure in organic synthesis⁶ and appreciably augments Wittig methodology.

The corresponding Wittig reagent, $\text{CH}_2=\text{PPh}_3$, reacts smoothly with both aldehydes and ketones to give methylenated products in high yield but with one subtle limitation. The problem cannot be detected with aldehydes because they react rapidly even at temperatures as low as -78°C , but ketones react more slowly, and an adjacent enolizable chiral center can be epimerized as a result of competitive reversible enolization. This limitation of the Wittig procedure has been recognized for some time⁷ and new methylenation methods^{7,8} that avoid enolization have been developed. However, the application of these methods is restricted either by low yields or by incompatibility with other functionality in the molecule. In the closest analogy to the present preparation of (+)-3-methylene-cis-p-menthane, one of these methods has been used for the methylenation of *l*-menthone⁹ but a yield of only 40% was obtained.

The $\text{Zn}/\text{CH}_2\text{Br}_2/\text{TiCl}_4$ procedure as originally reported¹⁰ has not been widely used. The active reagent was generated and trapped by the carbonyl compound in situ at room temperature. Long reaction times were required and as a consequence the substrate was exposed for long periods to TiCl_4 , severely limiting the usefulness of the procedure. The discovery⁴ that the active reagent was stable at low temperature and could be preformed extends the utility and scope of the reaction enormously. This reagent reacts rapidly

with ketones at room temperature with considerably improved yields and selectivities.

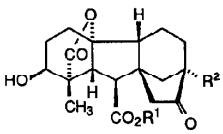
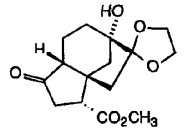
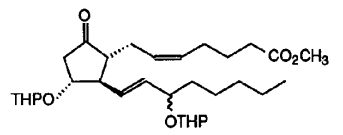
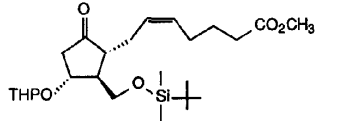
The non basic nature of the reagent makes it useful in other applications. It has, for example, also proved useful for the methylenation of the gibberellin norketone⁴ (Table I) without the need for protection of the readily epimerized 3 β -OH. The use of CD₂Br₂⁴ allows the introduction of =CD₂ without scrambling of the label.

The Zn/CH₂Br₂/TiCl₄ reagent is superior to other non-basic methylenation reagents. Furthermore the long shelf-life at low temperatures, together with the ease of workup, render it an appealing alternative to the Wittig method for the methylenation of ketones in general.

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Table I. Methylenation of Ketones with $\text{Zn/CH}_2\text{Br}_2/\text{TiCl}_4$

Substrate	Isolated Yield, %	Ref.
 <p> $\text{R}^1 = \text{R}^2 = \text{H}$ $\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{H}$ </p>	<p>80</p> <p>93</p>	2
	90	2
	80	4b
	81	4b

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-Isomenthone: Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)- (9);
(1196-31-2)

(+)-Isomenthol: Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2 β ,5 β)]-
(9); (23283-97-8)

Potassium dichromate: Dichromic acid, dipotassium salt (8); Chromic acid,
dipotassium salt (9); (7778-50-9)

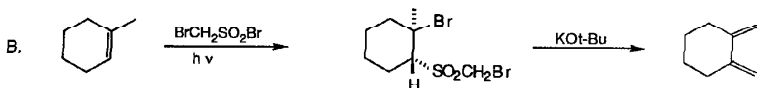
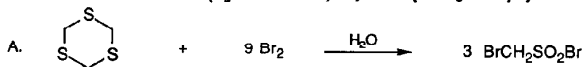
Zinc (8,9); (7440-66-6)

Dibromomethane: Methane, dibromo- (8,9); (74-95-3)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

Dichloromethane: Methane, dichloro- (8,9); (75-09-2)

**A GENERAL SYNTHETIC METHOD FOR THE PREPARATION OF CONJUGATED DIENES
FROM OLEFINS USING BROMOMETHANESULFONYL BROMIDE: 1,2-DIMETHYLENECYCLOHEXANE
(Cyclohexane, 1,2-bis(methylene)-)**



Submitted by Eric Block and Mohammad Aslam.¹

Checked by Jeffrey C. Weber and Leo A. Paquette.

1. Procedure

A. Bromomethanesulfonyl bromide. A 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, pressure-equalized dropping funnel, and a thermometer is charged with 100 g (0.73 mol) of sym-trithiane (Note 1) suspended in 600 mL of water. Bromine (1136 g, 7.1 mol) is added with stirring while keeping the flask temperature around 40°C (Note 2). After the addition of half of the bromine, 600 mL of water is added and bromine addition is continued. After all of the bromine has been added, the reaction mixture is stirred for 0.25 hr. The mixture is transferred to a 4-L separatory funnel, the lower organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of methylene chloride (Note 3). The organic extracts are combined, washed with one 100-mL portion of cold 5% sodium bisulfite solution and with 100 mL of water, dried over anhydrous magnesium sulfate, and concentrated at room temperature with a rotary

evaporator to a light yellow oil. Distillation using a short Vigreux column affords 218-249 g (42-48%) of bromomethanesulfonyl bromide as a light yellow oil, bp 68-69°C (0.65 mm) (Notes 4, 5).

B. *1-Bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane*. Four Pyrex test tubes (2.5 x 20 cm) are charged with 1-methylcyclohexene (5.0 g per test tube; total weight 20.0 g, 0.21 mol) (Note 6). Methylene chloride (12 mL) is added to each test tube which is cooled in ice. An ice-cold solution of bromomethanesulfonyl bromide (13.6 g of bromomethanesulfonyl bromide per test tube; total weight 54.4 g, 0.23 mol) in methylene chloride (12 mL) is added to each test tube with mixing at 0°C (Note 7). The test tubes are attached with the help of several rubber bands to a Pyrex immersion well equipped with a 450-W mercury lamp (Note 8). The immersion well is cooled by circulation of ice water (Note 9) and immersed in a cooling bath maintained at -15°C. The reaction mixture is irradiated for 2 hr. Solid potassium carbonate (1.5 g) is added to each test tube and the contents of the test tubes are filtered through a small column with a glass wool plug into a 250-mL round-bottomed flask. Methylene chloride is removed, first on a rotary evaporator and then with a vacuum pump (1 mm), to give an oil which gradually solidifies (68.3 g, 98%). Recrystallization from 95% ethanol (100 mL) gives white crystals (54.3 g, 78%) (Note 10), mp 59-61°C (Note 11).

C. *1,2-Dimethylenecyclohexane*. An oven-dried, 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, pressure-equalized dropping funnel, and a stopper is charged with potassium tert-butoxide (59.5 g, 0.53 mol) (Note 12) dissolved in tert-butyl alcohol-tetrahydrofuran (9:1, 400 mL total) (Note 13) and cooled in ice. A solution of 1-bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane (54.0 g, 0.16 mol) in tert-butyl alcohol-tetrahydrofuran (9:1, 100 mL) (Note 14) is added dropwise over a 1-hr

period. After the addition is complete the reaction mixture is stirred at room temperature for 0.5 hr and then poured into a 2-L separatory funnel containing 500 mL of water. This solution is extracted with two 150-mL portions of pentane. The combined pentane extracts are washed eight times with water (500 mL) (Note 15), dried over anhydrous magnesium sulfate and filtered. The pentane is removed by distillation at atmospheric pressure using an efficient Vigreux column and the residue is distilled under reduced pressure to give 11.4 g (65%) of 1,2-dimethylenecyclohexane as a colorless liquid, bp 69-70°C (90 mm) (lit² 60-61°C, 90 mm) (Notes 16 and 17).

2. Notes

1. Sym-Trithiane is made as described by Bost and Constable³ and is used without purification. It can be purchased from Aldrich Chemical Company, Inc.

2. This is an exothermic reaction, no outside heating is required. If the temperature goes above 40°C, the flask is cooled by ice/water.

3. In the first of these extractions, the upper phase is the organic one. In the second extraction, the organic layer is at the bottom.

4. The product has refractive index n_D^{20} 1.5706 and spectral properties as follows: IR (neat) cm^{-1} : 3040 (vs), 2960 (vs), 1362 (vs), 1205 (s), 1160 (vs), 1105 (m), 830 (s), 680 (s); ¹H NMR (CDCl₃, 60 MHz) δ : 5.05 (s).

5. The product can be synthesized on a much smaller scale with no loss in yield simply by reducing the quantities as desired.

6. 1-Methylcyclohexene was obtained from the Aldrich Chemical Company, Inc. and was distilled before use.

7. On occasion bromomethanesulfonyl bromide undergoes spontaneous, exothermic addition to olefins. While this problem was not encountered with 1-methylcyclohexene, it is desirable to mix the reagents at low temperature to avoid a possible vigorous spontaneous reaction and to maximize the yield of adduct.

8. The apparatus should be shielded to avoid exposure to ultraviolet light. The immersion well, lamp, and the requisite transformer are available from Hanovia Lamp Division, Canrad-Hanovia Inc., 100 Chestnut Street, Newark, NJ 07105. The test tubes are positioned so as to be as close as possible to the lamp.

9. A "Little Giant" submersible pump (available from Little Giant Pump Co., Oklahoma City, OK) is used to circulate ice water through the immersion well.

10. The first crop (47.0 g) is followed by two other crops (5.2 and 2.1 g) obtained by concentrating and cooling the mother liquor.

11. The spectral properties are as follows: IR (KBr disc) cm^{-1} : 2960 (s), 1450 (m), 1380 (s), 1315 (vs), 1205 (s), 1140 (vs), 1090 (vs), 745 (s); ^1H NMR (300 MHz, CDCl_3) δ : 1.56-1.82 (m, 4 H, CH_2), 2.08-2.41 (m, 4 H, CH_2), 2.15 (s, 3 H, CH_3), 3.96 (dd, 1 H, CHSO_2), 4.58 (AB quartet, 2 H, $J_{\text{AB}} = 11$, CH_2Br); ^{13}C NMR (CDCl_3) δ : 22.66, 23.25, 24.27, 29.72, 43.69, 44.39, 65.81, 67.21.

12. Potassium tert-butoxide can be obtained from Aldrich Chemical Company, Inc.

13. The tert-butyl alcohol and tetrahydrofuran are distilled from calcium hydride prior to use.

14. Warming is required to dissolve the solid in this solvent.

15. The first four washings are done with gentle agitation to avoid emulsion formation.

16. The first cut of the distillate (ca. 1-2 mL) coming below 60°C was discarded.

17. The physical properties of the product are as follows: n_D^{20} 1.4722; IR (liquid film) cm^{-1} : 3090 (s), 2940 (s), 2870 (s), 1635 (s), 1440 (s), 895 (vs); ^{13}C NMR (CDCl_3) δ : 26.85, 35.37, 107.78, 149.68; GLC analysis (50 m OV-101 fused silica capillary column obtained from Perkin Elmer, Inc.) showed the product to be 90-93% pure. The material has an ^1H NMR spectrum corresponding to that reported in the literature:⁴ (300 MHz, CDCl_3) δ : 1.62-1.66 (m, 4 H, CH_2), 2.24-2.27 (m, 4 H, CH_2), 4.64-4.65 (m, 2 H, vinyl CH), 4.92-4.93 (m, 2 H, vinyl CH).















3. Discussion

This procedure illustrates a recently published, simple, general method for the synthesis of conjugated dienes from olefins.⁵ The scope of the reaction is shown in Table I.⁵ In most of these examples hydrogen bromide elimination can be effected by stirring a solution of the olefin-bromo-methanesulfonyl bromide adduct in methylene chloride with one equivalent of triethylamine at room temperature. Only two equivalents of the more costly potassium tert-butoxide are then needed in the second elimination step; the yields using the two-base procedure are generally superior to that obtained using only potassium tert-butoxide.

1,2-Dimethylenecyclohexane is a useful diene for Diels-Alder reactions^{6,7,8} which has previously been synthesized in 11-77% yield in multistep procedures from cis-1,2-cyclohexanedicarboxylic anhydride⁶ or acid,⁷ from diethyl phthalate,² or from cyclohexanone.⁴

1. Department of Chemistry, State University of New York at Albany, Albany, NY 12222. This work was made possible by grants from the National Science Foundation, the Petroleum Research Fund administered by the American Chemical Society, the Société Nationale Elf Aquitaine and the John Simon Guggenheim Memorial Foundation.
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Table I. Diene Synthesis via the Vinylogous Ramberg-Bäcklund Reaction

	Olefin	Product (Isomer Ratio ^a)	Yield, % ^b
1	$C_4H_9CH=CH_2$	$C_9H_7CH=CHCH=CH_2$ (2:1)	38
2	$C_6H_{13}CH=CH_2$	$C_9H_{11}CH=CHCH=CH_2$ (2:1) ^c	61
3	(E)- $C_4H_9CH=CHC_4H_9$	(E)- $C_3H_7CH=CHC(C_4H_9)=CH_2$	68 ^d
4	(E)- $C_5H_{11}CH=CHCH_3$	(E)- $C_4H_9CH=CHC(CH_3)=CH_2$ + $CH_2=CHC(C_5H_{11})=CH_2$	52 15
5			53
6			74
7			75
8			41 ^e
9			31 ^e
10			49 ^o
11			43 ^o
12	$PhCH_2CH=CH_2$	$PhCH=CHCH=CH_2$ (1:8)	65
13	$PhOCH_2CH=CH_2$	$PhOCH=CHCH=CH_2$ (9:1)	54
14	$HO(CH_2)_6CH=CH_2$	$HO(CH_2)_6CH=CHCH=CH_2$ (5:1)	86
15	$(CH_3)_3SiCH_2CH=CH_2$	$(CH_3)_3SiCH=CHCH=CH_2$ (1:10)	41
16	$CH_2=CH(CH_2)_6CH=CH_2$	$CH_2=CH(CH_2)_5CH=CHCH=CH_2$	49 ^{f,g,h}
17	$CH_2=CH(CH_2)_6CH=CH_2$	$CH_2=CHCH=CH(CH_2)_4CH=CHCH=CH_2$	40 ^j
18	$(CH_3)_2Si(CH_2CH=CH_2)_2$	$(CH_3)_2Si(CH=CHCH=CH_2)_2$	38 ⁱ

^a(Z):(E) ratio. ^bOverall yield of distilled product. ^c(Z):(E) ratios 5:1 and 1:16 from (E)- and (Z)-1-octenylbromomethyl sulfones, respectively (59-61% overall distilled yields).² ^dAnalysis by GLC indicated <1% (Z) isomer. ^eEt₃N step omitted. ^fIsomers not resolved by GLC. ^gTwo equiv. of diene used. ^hIncludes ca. 5% of 1,3,9,11-dodecatetraene. ⁱTwo molar equiv. of 1 used. ^jCa. 80% (Z,Z).

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,2-Dimethylenecyclohexane: Cyclohexane, 1,2-dimethylene (8); Cyclohexane, 1,2-bis(methylene)- (9); (2819-48-9)

Bromomethanesulfonyl bromide: Methanesulfonyl bromide, bromo- (9); (54730-18-6)

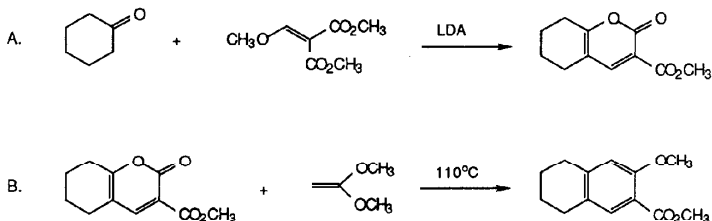
Sym-Trithiane: S-Trithiane (8); 1,3,5-Trithiane (9); (291-21-4)

Bromine (8,9); (506-68-3)

1-Methylcyclohexene: Cyclohexene, 1-methyl- (8,9); (591-49-1)

PREPARATION AND INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF AN
ELECTRON-DEFICIENT DIENE: METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2H-1-
BENZOPYRAN-3-CARBOXYLATE

(2H-1-Benzopyran-3-carboxylic acid, 5,6,7,8-tetrahydro-2-oxo-, methyl ester)



Submitted by Dale L. Boger and Michael D. Mullican.¹

Checked by Drew B. Burns and K. Barry Sharpless.

1. Procedure

A. *Methyl 2-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate.* A dry, 500-mL, round-bottomed flask with a sidearm containing a magnetic stirring bar is fitted with a septum and a three-way stockcock equipped with an argon-filled balloon (Note 1). The air in the flask is replaced with argon (Note 2). Tetrahydrofuran (100 mL, Note 3) and diisopropylamine (4.7 g, 46 mmol, Note 4) are introduced into the flask through the septum using dry syringes (Note 5). The flask is immersed in an ice-water bath and a 2.8 M solution of butyllithium in hexane (17 mL, 46 mmol, Note 6) is added to the

stirred solution using a syringe (10 min). The yellow solution is allowed to stir at 0°C for an additional 15 min. The resulting solution containing lithium diisopropylamide is immersed in a dry ice-2-propanol bath (-78°C) and a solution of cyclohexanone (3.74 g, 38.1 mmol, Note 7) in tetrahydrofuran (50 mL) is added using a syringe (30 min). The reaction is allowed to warm slowly to -5°C over 1.75 hr. The resulting solution containing the lithium enolate of cyclohexanone is recooled to -30°C to -25°C and a solution of dimethyl methoxymethylenemalonate (8.1 g, 46 mmol, Note 8) in tetrahydrofuran (20 mL) is added using a syringe (15 min). The reaction is allowed to warm to ambient temperature over 3.5 hr (Note 9). The reddish-orange solution is poured slowly onto aqueous 5% hydrochloric acid (300 mL) and the resulting yellow solution is extracted with methylene chloride (4 x 80 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to approximately 15 mL. The solution is applied to a medium pressure liquid chromatography column (25 x 500 mm, Note 10) packed with silica gel and 30% ethyl acetate-hexane. The eluant (30% ethyl acetate-hexane) is passed through the column at a rate of 20 mL/min; 20-mL fractions are collected (Note 11). The fractions are analyzed by thin-layer chromatography on analytical silica gel plates containing UV indicator (ethyl ether eluant). The fractions containing the product are combined and concentrated under reduced pressure to give 4.9 g (62%, 62-68%) of methyl 2-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate as a white solid: mp 107-108°C (ethyl acetate-hexane, Note 12).

B. *6-Methoxy-7-methoxycarbonyl-1,8,8,4-tetrahydronaphthalene.* 1,1-Dimethoxyethylene (1.1 g, 12.5 mmol, Note 13) is added to a solution of methyl 2-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate (507 mg, 2.44 mmol) in dry toluene (2.5 mL, Note 14) in a dry, 11 x 13 mm, resealable glass tube

(Note 15). The tube is flushed with argon and sealed with a Teflon plug. The reaction is warmed at 110°C in an oil bath for 15 hr (Note 16). The reaction is cooled and concentrated under reduced pressure. Purification of the product is effected by gravity chromatography on a 1.5 x 16-cm column of silica gel (30% ethyl ether-hexane eluant) collecting 5-mL fractions (Note 17). The fractions are analyzed by thin-layer chromatography (50% ethyl ether-hexane eluant) and those containing the product are combined and concentrated under reduced pressure to give 451 mg (84%, 84-86%) of 6-methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene as a white solid: mp 98.5-99.5°C (methanol-water, Note 18).

2. Notes

1. The flask containing the stirring bar was dried at 120°C in an oven for several hours. The warm flask was fitted with a septum and a three-way stopcock.
2. This procedure is described in detail in *Org. Synth.* **1971**, 51, 39.
3. Tetrahydrofuran was distilled from benzophenone ketyl under a nitrogen atmosphere.
4. Diisopropylamine was distilled from calcium hydride under a nitrogen atmosphere and stored over activated 3 Å sieve pellets.
5. The hypodermic syringes and needles were dried for several hours in an oven at 120°C and allowed to cool to ambient temperature in a desiccator.
6. Butyllithium was purchased from Aldrich Chemical Company, Inc.
7. Cyclohexanone was distilled before use.

8. Technical grade dimethyl methoxymethylenemalonate was purchased from Fluka Chemical Corporation and was purified by recrystallization from ether (2x), mp 43.0-44.0°C. It can be prepared by the procedure described for diethyl ethoxymethylenemalonate.²

9. Gradual warming to room temperature over 3.5 hr is necessary to ensure reasonable yields. Shorter times result in significantly lower yields.

10. The use of medium pressure liquid chromatography is described by Meyers.³

11. The checkers found that MPLC can be replaced by ordinary flash chromatography (30% EtOAc-hexane eluant, 6-cm I.D. column, ~ 200-240 g of flash-grade silica gel 230-400 mesh, 250-mL fractions). The crude product was dissolved in CH_2Cl_2 to which was added several grams of silica gel. This mixture was concentrated under reduced pressure and the resulting solid was applied to the top of the column.

12. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 1.80 (m, 4 H, CH_2CH_2), 2.46 (m, 4 H, $\text{CH}_2\text{CH}_2\text{C}=\text{CH}_2$), 3.86 (s, 3 H, $-\text{CO}_2\text{CH}_3$), 7.99 (s, 1 H, vinyl); IR (CHCl_3) ν_{max} cm^{-1} : 3040, 2975, 1765, 1745, 1555, 1270, 1220, 1155.

13. 1,1-Dimethoxyethylene was purchased from Wiley Organics and used without further purification.

14. Toluene was distilled from calcium hydride under a nitrogen atmosphere.

15. The resealable glass tube was fabricated from a chromatography column purchased from Ace Glass Company. The tube was permanently sealed on one end and the other end remained internally threaded. A solid, threaded, Teflon plug equipped with an O-ring was used to seal the tube. Various sizes of such tubes are now available from Ace Glass Company.

16. *Caution: The reaction should be run behind a shield in a fume hood for protection in case of explosion. Pressure will build up in the tube since 1,1-dimethoxyethylene boils at 89°C and carbon dioxide is formed.*

17. The checkers found that gravity chromatography can be replaced by ordinary flash chromatography (30% ethyl ether-hexane eluant, 2.5-cm I.D. column ~ 40 g of flash grade silica gel, 20-mL fractions). In at least one case, the checkers found that pure product could be isolated in high yield (98%) without recrystallization.

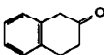
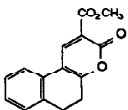
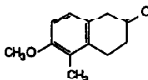
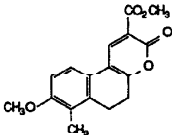

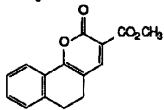

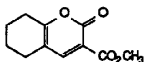

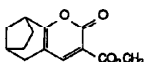
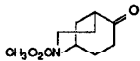
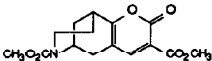
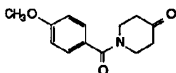
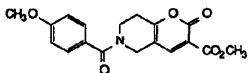

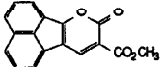
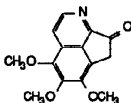
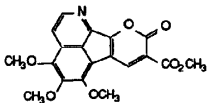
18. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 1.80 (m, 4 H, CH_2CH_2), 2.75 (m, 4 H, $\text{CH}_2\text{CH}_2\text{C}=\text{C}$), 3.86 (s, 6 H, $-\text{OCH}_3$ and $-\text{CO}_2\text{CH}_3$), 6.65 (s, 1 H, C-5 H), 7.53 (s, 1 H, C-8 H); IR (CHCl_3) ν_{max} cm^{-1} : 3040, 2970, 1725, 1610, 1280, 1080, 1114. t_b 99-100°C.

3. Discussion

This procedure describes the preparation and inverse electron demand ($\text{LUMO}_{\text{diene}}$ controlled)⁵ Diels-Alder reaction of an electron-deficient diene. While extensive studies on the preparative utility of the normal ($\text{HOMO}_{\text{diene}}$ controlled)⁵ Diels-Alder reaction have been detailed, few complementary studies on the preparative value of the inverse electron demand Diels-Alder reaction have been described.⁶ Table I details representative 3-carbomethoxy-2-pyrones which have been prepared by procedures similar to that described herein and Tables II and III detail their inverse electron demand Diels-Alder reactions with electron-rich dienophiles.

A use of the $\text{LUMO}_{\text{diene}}$ controlled Diels-Alder reactions of 3-carbomethoxy-2-pyrones in the preparation of a full range of oxygenated aromatics [e.g., benzene, 1-, 2-, or 3-phenol, symmetrical and unsymmetrical

Table I. Preparation of 3-Carbomethoxy-2-pyrones.^{6f}

	Ketone	Method, % Yield	3-Carbomethoxy-2-pyrone	2
1a		A, 73%		2a
1b		A, 81%		2b
1c		B, 90%		2c
1d		B, 84%		2d
1e		B, 62%		2e
1f		B, 56%		2f
1g		B, 35% C, 59%		2g
1h		C, 47% D, 96%		2h
1i		D, 62%		2i

^aMethod A: The enolate of 1 was generated with 2.2 equiv of NaH in THF (0.2 M) at 0 to 25°C. Method B: the enolate of 1 was generated with 1.2 equiv of LDA in THF (0.2 M) at -78 to -5°C. Method C: the enolate of 1 was generated with 1.2 equiv of LDA in THF (0.2 M) at -78 to -5°C and closure to the α-pyrone was effected with acetic anhydride treatment at 100 to 130°C. Method D: the enolate of 1 was generated with 2.2 equiv of NaH in THF (0.2 M) at 0 to 25°C and closure to the α-pyrone was effected with catalytic p-toluenesulfonic acid treatment in refluxing toluene with distillative removal of methanol.

Table II. Diels-Alder Reaction of 3-Carbomethoxy-2-pyrones (2) with
1,1-Dimethoxyethylene: Salicylate Formation

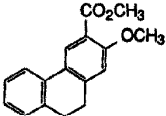
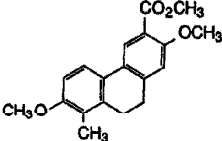
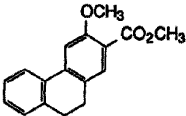
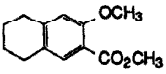
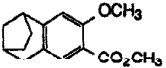
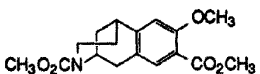
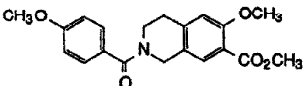
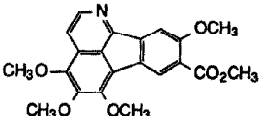

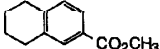


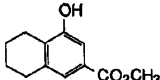

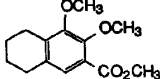
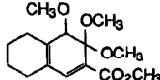

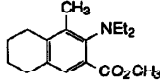
3-Carbomethoxy- 2-pyrone (2)	Conditions equiv time hr(temp. °C)	Product	% Yield ^{6f}
2a	8.5, 22(140)		59%
2b	10.0, 21(140)		75%
2c	10.0, 15(120)		78%
2d	5.5, 15(110) 5.0, 96(25), CH ₂ Cl ₂ cat. Ni(acac) ₂		86% 50%
2e	6.0, 12(95)		90%
2f	10.0, 13(120)		80%
2g	10.0, 24(120)		91%
2i	8.0, 5(120)		83%

Table III. Diels Alder Reactions of 3-Carbomethoxy-2-pyrone (2d)^{6f}.

Entry	Dienophile (equiv.)	Conditions temp. °C (time, hr)	Product(s)	% Yield
1	 (3.0)	160(42)		98%
2	 (5.0)	145(43)	" "	51%
3	 (5-10.0)	180(40)		83%
4	 (5.0)	150(78); cat. CH ₃ SO ₃ H or		57%
	(10.0)	150(84); cat. DBU 150(12)	" "	51%
5	" " (10.0)	120(59)		61%
6	 (2.0)	150(17)		43%

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 2-oxo-5,6,7,8-tetrahydro-2H-1-benzopyran-3-carboxylate:

2H-1-Benzopyran-3-carboxylic acid, 5,6,7,8-tetrahydro-2-oxo-, methyl ester
(11); (85531-80-2)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Cyclohexanone (8,9); (108-94-1)

Dimethyl methoxymethylenemalonate: Malonic acid, (methoxymethylene)-,
dimethyl ester (8); Propanedioic acid, (methoxymethylene)-, dimethyl ester
(9); (22398-14-7)

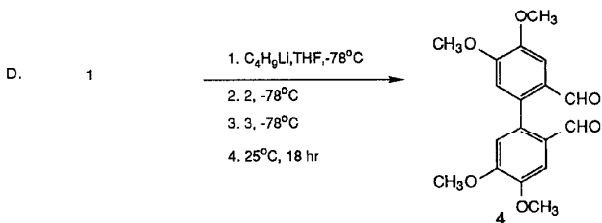
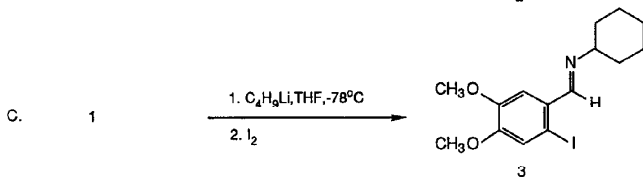
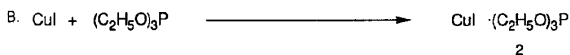
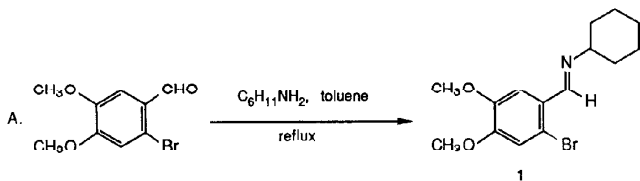
6-Methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene: 2-Naphthalene-
carboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester (10);
(78112-34-2)

1,1-Dimethoxyethylene: Ethene, 1,1-dimethoxy- (9); (922-69-0)

AMBIENT TEMPERATURE ULLMANN REACTION: 4,5,4',5'-TETRAMETHOXY-

1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE

([1,1'-Biphenyl]-2,2'-dicarboxaldehyde, 4,4',5,5'-tetramethoxy-)



Submitted by F. E. Ziegler, K. W. Fowler, W. B. Rodgers, and R. T. Wester.¹

Checked by Tetsuji Oshima and Ryoji Noyori.

1. Procedure

CAUTION! Aqueous sodium cyanide is used in this procedure. All operations should be conducted in a well-ventilated hood and rubber gloves should be worn.

A. 6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine (1). A 2-L. three-necked flask is equipped with a Dean-Stark trap, reflux condenser, magnetic stirrer, and nitrogen inlet. The vessel is purged with nitrogen and charged with 40.0 g (0.16 mol) of 6-bromo-3,4-dimethoxybenzaldehyde (6-bromo-veratraldehyde) (Note 1), 22.4 mL (0.20 mol) of cyclohexylamine (Note 2), and 800 mL of toluene. The mixture is refluxed for 16 hr (Note 3). The solution is cooled to room temperature and the solvent is removed on a rotary evaporator. The residual crystalline mass is recrystallized from a 3:1 hexane-methylene chloride mixture (1.5 L) to provide 48.4-51.4 g of the imine **1** as white crystals in two crops (mp 172-172.5°C)² (Note 4).

B. Cuprous iodide-triethyl phosphite complex (2). (Note 5). A 1-L, round-bottomed flask equipped with a magnetic stirrer and reflux condenser is flame-dried under nitrogen. The vessel is charged with 38.2 g (0.20 mol) of cuprous iodide, 33.4 mL (0.20 mol) of triethyl phosphite (Note 6) and 400 mL of dry toluene (distilled from CaH₂). The mixture is stirred at 80°C for 8 hr, cooled to room temperature, and filtered under reduced pressure on a pad of Celite. The solvent is removed from the filtrate successively with a rotary evaporator and briefly (15 min) under high vacuum. The residual solid is recrystallized from ether (25 mL) to yield 41.1-49.9 g (57.4-69.8%) of cuprous iodide-triethyl phosphite complex in two crops, mp 114-115°C.

C. *6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine* (3). A 1-L, three-necked flask is equipped with a Claisen adapter (Note 7), Trubore stirrer, nitrogen inlet, and glass stoppers. The flask is thoroughly flame-dried under nitrogen. To the cooled flask is added 14.0 g (0.043 mol) of cyclohexylimine 1 and the glass stoppers are replaced by an alcohol thermometer and a rubber septum. Tetrahydrofuran (400 mL) (Note 8) is added via syringe through the septum and the resultant mixture is stirred at room temperature (27°C) for 30 min to effect solution. The solution is cooled to -78°C in a dry ice-acetone bath (Note 9). A solution of butyllithium in hexane (30.9 mL, 1.53 M, 0.047 mol) (Note 10) is added by syringe over 10 min at such a rate as to maintain the temperature below -75°C (Note 11). As the butyllithium is added the precipitate slowly dissolves leaving a clear, golden-yellow solution which is stirred for 15 min after the addition is complete. A solution of 27.0 g (0.11 mol) of iodine dissolved in 50 mL of dry THF is added via syringe to the reaction mixture at such a rate as to maintain the temperature below -70°C. The iodine solution (20-25 mL) is added until the red iodine color persists; precipitation also occurs. The mixture is warmed to room temperature, poured into 400 mL of water, and extracted with methylene chloride (5 x 400 mL). The combined organic extracts are dried (anhydrous MgSO_4), filtered, and concentrated on a rotary evaporator to 200 mL, and then washed with 200 mL of aqueous saturated sodium sulfite solution. The organic phase is redried, filtered, and concentrated. The solid residue is recrystallized from a 1:4 chloroform-hexane mixture (300 mL) to afford 12.6-13.5 g (78.6-85.0%) yield of 6-iodoveratraldehyde cyclohexylimine as white crystals, mp 180-181°C² (Note 4).

D. 4,5,4',5'-Tetramethoxy-1,1'-biphenyl-2,2'-carboxaldehyde (4). The metalation procedure described in Section C is repeated using a 3-L flask, 18.4 g (0.056 mol) of 6-bromoveratraldehyde cyclohexylimine (1), 575 mL of tetrahydrofuran, and 40.6 mL (1.53 M, 0.062 mol) of butyllithium. After the metalation is complete at -78°C, the septum is replaced by a glass stopper. Solid cuprous iodide-triethyl phosphite complex (30.3 g, 0.085 mol) is added to the vessel at -78°C in one portion, immediately giving a green solution. The mixture is stirred for an additional 30 min. After the first 15 min, the solution turns a brownish-orange to red color. Solid 6-iodoveratraldehyde cyclohexylimine (3) (21.0 g, 0.056 mol) is added in one portion to produce an orange suspension. The reaction mixture is allowed to warm to room temperature (27°C) during which time the mixture becomes dark brown. The reaction mixture is stirred for 18 hr at room temperature. The reaction mixture is diluted with 600 mL of methylene chloride and 850 mL of 15% aqueous acetic acid and stirred vigorously for 17 hr. The yellow solution is transferred to a 4-L separatory funnel and the layers are separated. The organic layer is dried (anhydrous magnesium sulfate), filtered, and concentrated on a rotary evaporator to 800 mL and then transferred to a 2-L separatory funnel. The organic solution is washed with 5% aqueous hydrochloric acid (5 x 100 mL) and saturated aqueous sodium bicarbonate solution (10 x 50 mL). [CAUTION: The final washings must be alkaline to avoid the liberation of hydrogen cyanide in the subsequent step.] The organic layer is washed twice with 500 mL of 10% aqueous sodium cyanide solution, once with 500 mL of saturated aqueous sodium bicarbonate, and twice with 500 mL of water. [CAUTION: The sodium cyanide washes should be bottled separately and labeled appropriately for approved disposal.] The organic layer is dried (anhydrous magnesium sulfate), filtered, and concentrated to provide 16.3-20.3

g of residue. Crystallization from a 1:3 methylene chloride-hexane mixture at 5°C affords 13.1-16.9 g (70.4-90.7%) of beige crystals of the biphenyl, mp 215-216°C (lit³ 214-215°C) after drying under high vacuum (0.1 mm) (Note 4).

2. Notes

1. 6-Bromo-3,4-dimethoxybenzaldehyde was purchased from the Aldrich Chemical Company, Inc. (Milwaukee) or readily prepared by bromination of veratraldehyde (Aldrich Chemical Company, Inc. or Tokyo Kasei).⁴

2. Cyclohexylamine (Aldrich Chemical Company, Inc. or Nakarai Chemicals) and all solvents and reagents (reagent grade) were used as received, unless otherwise specified.

3. The water level in the trap remains constant after this period of time.

4. Spectral characterization; ¹H NMR (CDCl₃). 6-Bromoveratraldehyde cyclohexylimine, δ: 1.07-1.82 (m, 10 H), 3.30 (m, 1 H, NCH), 3.89 (s, 3 H, OCH₃) 3.92 (s, 3 H, OCH₃), 6.97 (s, 1 H), 7.55 (s, 1 H), and 8.54 (s, 1 H, N=CH); 6-Iodoveratraldehyde cyclohexylimine, δ: 1.07-1.82 (m, 10 H), 3.31 (m, 1 H, NCH), 3.88 (s, 3 H, OCH₃), 3.92 (s, 3 H, OCH₃), 7.22 (s, 1 H), 7.53 (s, 1 H), and 8.32 (s, 1 H, N=CH); 4,5,4',5'-Tetramethoxy-1,1'-biphenyl-2,2'-dicarboxaldehyde, δ: 3.96 (s, 6 H, OCH₃), 4.01 (s, 6 H, OCH₃), 6.80 (s, 2 H), 7.56 (s, 2 H), and 9.67 (s, 2 H, CHO).

5. This method was adapted from the procedure of Nishizawa.⁵ The complex is reported to have mp 109-110°C.⁶

6. Cuprous iodide was purchased from Alfa Products, Morton/Thiokol Inc. or Kishida Chemicals and triethyl phosphite from the Aldrich Chemical Company, Inc. or Nakarai Chemicals.

7. The offset neck of the adapter was fitted with the nitrogen inlet and the other neck with a glass stopper which was eventually replaced with a thermometer.

8. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen in all applications.

9. The bromide, 1, precipitated during the cooling.

10. Butyllithium was purchased from Alfa Products, Morton/Thiokol Inc. or Mitsuwa Pure Chemicals and was standardized by the method of Kofron.⁷

11. Alcohol thermometers were found not to read temperatures accurately. A temperature of -78°C designates the lowest temperature to which a large dry ice-acetone bath cools the reaction mixture. The temperature -75°C signifies a 3° rise in temperature.

3. Discussion

The Ullmann reaction has been traditionally conducted at elevated temperatures ($100\text{--}250^{\circ}\text{C}$), with or without solvent, in the presence of copper powder. Often the quality of copper can be extremely important to the success of the reaction.⁸ Aromatic bromides and halides which bear ortho-substituted electron-withdrawing groups undergo coupling at the low end of the temperature range. Cross coupling is best accomplished when only one of the aryl halides bears an electron-withdrawing group.⁹ In such instances, an excess of the aryl halide without the electron-withdrawing group may have to be employed.¹⁰

Nickel(0) reagents have been employed in the symmetrical coupling of aryl halides in sterically unencumbered cases.^{11,12} An efficient cross coupling reaction between an arylzinc halide and an ortho-iodoarylimine under mild conditions mediated by Ni(0) has been reported.¹³ Thallium(III)

trifluoroacetate has been employed in the symmetrical coupling of aromatic ethers.¹⁴ The use of diazonium salts in the formation of unsymmetrical biphenyls has been reviewed.¹⁵

The present method permits both symmetrical and unsymmetrical coupling to occur at room temperature. It is necessary for a substituent (nitrogen or sulfur) to be situated ortho to the halogen so that the heteroatom can chelate well with copper. This requirement must be fulfilled in both reacting partners. The organolithium species may be generated by metal-hydrogen or metal-halogen exchange. The coupling works well in sterically congested compounds, and only for aryl iodides. o-Iodoaldehydes may also be prepared by direct iodination of aromatic aldehydes.^{12,16} Representative applications of this reaction are provided in the Table.

Table I. Ambient Temperature Ullman Reaction

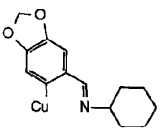
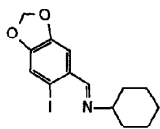
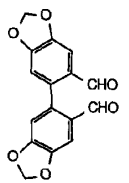
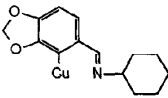
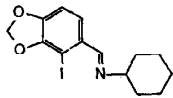
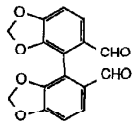
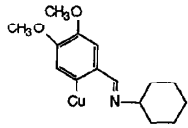
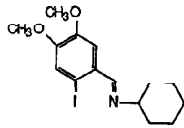
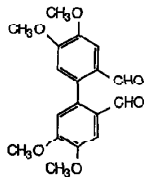
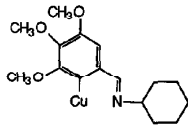
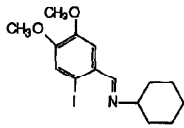
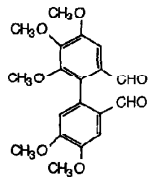
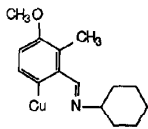
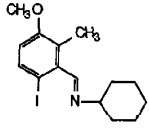
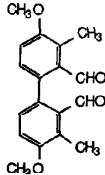
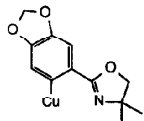
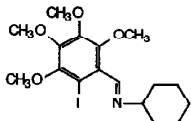
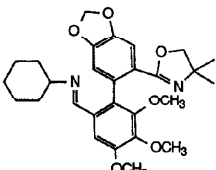
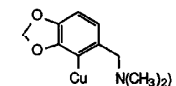
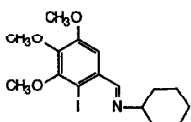
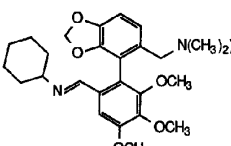
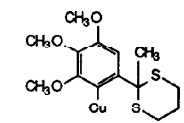
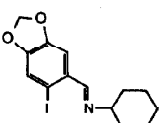
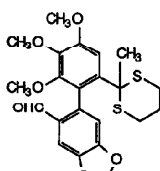
Organocopper	Iodide	Biphenyl	Yield (%) ^{ref}
			57 ²
			44 ²
			76(62) ²
			63 ²
			88 ¹²

Table I. (continued) Ambient Temperature Ullman Reaction

Organocopper	Iodide	Biphenyl	Yield (%) ^{ref}
			54 ²
			48 ²
			63 ²

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4,5,4',5'-Tetramethoxy-1,1'-biphenyl-2,2'-dicarboxaldehyde:

[1.1'-Biphenyl]-2,2'-dicarboxaldehyde, 4,4',5,5'-tetramethoxy- (9);
(29237-14-7)

6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine,

N-[(2-bromo-4,5-dimethoxyphenyl)methylene]- (10); (73252-55-8)

6-Bromo-3,4-dimethoxybenzaldehyde: Benzaldehyde, 2-bromo-4,5-dimethoxy-
(9); (5392-10-9)

Cyclohexylamine (8); Cyclohexanamine (9); (108-91-8)

Cuprous iodide: Copper iodide (8,9); (7681-65-4)

Triethyl phosphite: Phosphorous acid, triethyl ester (8,9); (122-52-1)

6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine,

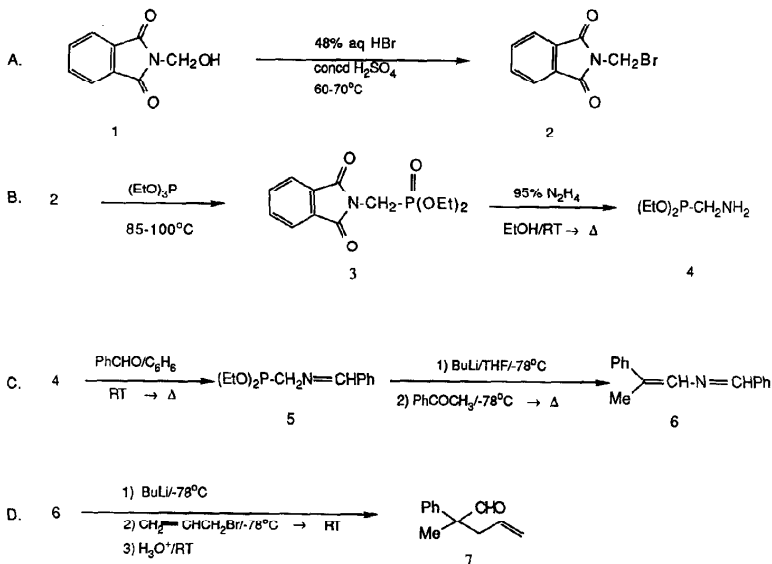
N-[(2-iodo-4,5-dimethoxyphenyl)methylene]- (10); (61599-78-8)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Iodine (8,9); (7553-56-2)

**GEMINAL ACYLATION-ALKYLATION AT A CARBONYL CENTER USING
DIETHYL N-BENZYLIDENEAMINOMETHYLPHOSPHONATE:
PREPARATION OF 2-METHYL-2-PHENYL-4-PENTENAL**

(4-Pentenal, 2-methyl-2-phenyl-)



Submitted by Steven K. Davidsen, Gerald W. Phillips,
and Stephen F. Martin.¹

Checked by Robert L. G. Aslarian, Max Tishler, and Andrew S. Kende.

1. Procedure

A. *N-Bromomethylphthalimide* (2). A 1-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer, a 125-mL pressure equalizing dropping funnel, and a thermometer. The flask is charged with 50.0 g (0.28 mol) of *N*-hydroxymethylphthalimide (Note 1) and 200 mL of 48% aqueous hydrobromic acid (Note 2). The flask is immersed in an ice bath, and 75 mL of concentrated sulfuric acid is added with stirring over a period of about 15 min (Note 3). Upon completion of the addition, the flask is removed from the ice bath, heated at 60-70°C for 5 hr and then cooled overnight in a refrigerator. The solid is collected by suction filtration using a 125-mm glass funnel with a coarse frit. The crude product is washed thoroughly with three 100-mL portions of cold water, two 50-mL portions of cold 10% aqueous ammonium hydroxide and finally with three 100-mL portions of cold water (Note 4). The crude product thus obtained is completely dried under reduced pressure at room temperature over phosphorus pentoxide to give 57.1-63.8 g (85-95%) of *N*-bromomethylphthalimide as a light tan solid, mp 142-147°C. Although the material thus obtained may be used in the next step without further purification, it may also be recrystallized from dry acetone, mp 147-148°C (lit., mp 148°C,² 148-149°C³) (Note 5).

B. *Diethyl phthalimidomethylphosphonate* (3). A 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an efficient reflux condenser (approximately 80-cm long) is charged with 51.2 g (0.21 mol) of dry *N*-bromophthalimide (2) and 43.1 g (0.26 mol) of freshly distilled triethyl phosphite (Note 6). The mixture is immersed in an oil bath and the temperature of the oil bath gradually increased over about 15 min to 85-100°C, whereupon the solid dissolves and a vigorous, exothermic reaction ensues

(Note 7). When the reaction has subsided, the oil bath is lowered and the condenser is removed. The flask is fitted for simple distillation, and ethyl bromide is distilled from the reaction mixture over a period of 3-4 hr by continued heating at 115°C (oil bath). The resulting light yellow oil is cooled to room temperature, whereupon it solidifies (Note 8). The crude product is collected by suction filtration and washed with three 100-mL portions of cold petroleum ether (bp 60-68°C) to give 50.1-56.3 g (80-90%) of diethyl phthalimidomethylphosphonate as white crystals, mp 60-63°C, which are used in the next step without further purification. Recrystallization of this material from diethyl ether/petroleum ether (bp 60-68°C) affords pure 3, mp 65-67°C (lit.,³ 67°C) (Note 9).

C. *Diethyl N-benzylideneaminomethylphosphonate* (5). A 2-L, two-necked, round-bottomed flask is equipped with a mechanical stirrer and a 125-mL pressure equalizing dropping funnel fitted with a calcium chloride drying tube. The flask is charged with 50.0 g (0.17 mol) of diethyl phthalimido-methylphosphonate (3) dissolved in 750 mL of absolute ethanol (Note 10). To this solution is then added 6.4 g (0.19 mol) of 95% hydrazine (Note 11) in 50 mL of absolute ethanol, and the resulting mixture is stirred overnight at room temperature. The dropping funnel is replaced with a reflux condenser bearing a calcium chloride drying tube, and the mixture is heated at reflux for 4 hr and then cooled to 0-5°C in an ice bath. The precipitated phthalhydrazide is collected by suction filtration and thoroughly washed with three 125-mL portions of benzene. The excess solvents and hydrazine are completely removed under reduced pressure on a rotary evaporator and then under high vacuum (Notes 12, 13). The crude diethyl aminomethylphosphonate (4)^{4,5} (Note 14) thus obtained is dissolved in 350 mL of reagent grade benzene, and the solution is cooled overnight in the refrigerator. Any additional

phthalhydrazide which precipitates is removed by suction filtration and washed with two 25-mL portions of benzene. The filtrate and washings are combined in a 1-L, one-necked flask equipped with magnetic stirring bar, and the solution is cooled to 5-10°C at which time 21.2 g (0.20 mol) of freshly distilled benzaldehyde is added in one portion with stirring. The mixture is stirred for 4 hr at room temperature, the flask is fitted with a Dean-Stark trap and a reflux condenser and heated overnight at reflux with constant removal of water. The solution is cooled to approximately room temperature, and the excess solvents are removed under reduced pressure. The crude product is purified by vacuum distillation, bp 145-149°C (0.05 mm), to give 37.5-40.2 g (84-90%) of pure diethyl N-benzylideneaminomethylphosphonate (5)^{6,7} as a light yellow oil (Note 15).

D. *2-Methyl-2-phenyl-4-pentenal* (7). A dry, 100-mL three-necked, round-bottomed flask with 14/20 joints is fitted with a magnetic stirrer, reflux condenser, and a rubber septum (Note 16). The flask is charged with 50 mL of anhydrous tetrahydrofuran (Note 17) and cooled to -78°C in a dry ice/isopropyl alcohol bath, and a solution of butyllithium (12.0 mmol) in hexane (Note 18) is added with stirring. To this stirred solution is added dropwise via syringe a solution of 3.06 g (12.0 mmol) of diethyl N-benzylideneamino-methylphosphonate (5) in 5 mL of anhydrous tetrahydrofuran, and the colored solution is stirred an additional hour at -78°C. A solution containing 1.20 g (10.0 mmol) of freshly distilled acetophenone in 5 mL of anhydrous tetrahydrofuran is added dropwise, and the cooling bath is removed. The solution is stirred for 1 hr at room temperature and then at reflux for 2 hr. After the solution is cooled to room temperature, it is poured into a 250-mL round-bottomed flask and the solvents are removed under reduced pressure on a rotary evaporator. The yellow residue is partitioned between

50 mL of ether and 50 mL of saturated sodium chloride. The layers are separated and the aqueous phase is extracted with three 25-mL portions of ether. The combined organic layers are washed with 50 mL of saturated sodium chloride and dried over magnesium sulfate. Magnesium sulfate is removed by filtration, and the excess solvents are then completely removed under reduced pressure on a rotary evaporator. The resulting yellow solid is dried under reduced pressure and transferred to a 100-mL two-necked, round-bottomed flask which is fitted with a magnetic stirring bar, a nitrogen inlet, and a rubber septum. The flask is charged with 50 mL of anhydrous tetrahydrofuran and flushed thoroughly with dry nitrogen. The resulting solution of the 2-azadiene 6 (Note 20) is cooled to -78°C , and a solution of butyllithium (12.0 mmol) in hexane is added dropwise via syringe. The deeply-colored solution is stirred at -78°C for 1 hr at which time 1.81 g (15.0 mmol) of freshly distilled allyl bromide (Note 21) is added. The cooling bath is removed, and the solution is stirred for 2 hr at room temperature. The reaction is added to 50 mL of 3 N aqueous hydrochloric acid, and the resulting heterogeneous mixture is stirred vigorously for 18 hr at room temperature. After the addition of 50 mL of saturated sodium chloride, the layers are separated, and the aqueous layer is extracted with three 75-mL portions of ether. The combined organic layers are washed with 75-mL portions of saturated aqueous sodium bicarbonate and saturated sodium chloride, and the washings are backwashed with a 50-mL portion of ether. The combined organic layers are dried over magnesium sulfate, and the excess solvents are removed under reduced pressure on a rotary evaporator. Distillation of the resulting yellow oil under reduced pressure gives 1.30-1.45 g (75-83%) of pure 2-methyl-2-phenyl-4-pentenal as a colorless liquid, bp $70-73^{\circ}\text{C}$ (0.1 mm) (Note 22).

2. Notes

1. Although N-hydroxymethylphthalimide may be purchased from Aldrich Chemical Company, Inc., it may also be prepared from phthalimide and 37% aqueous formaldehyde.⁸ Material prepared in this way should be dried at room temperature under reduced pressure over phosphorus pentoxide.

2. Aqueous 48% hydrobromic acid should be purchased from Eastman Organic Chemicals since that obtained from other sources tends to give, for unknown reasons, less satisfactory results.

3. The temperature should not be allowed to exceed 30°C during the addition.

4. Removal of *all* of the hydrobromic acid by washing is critical to the success of the next reaction. If the filtrate is not basic after washing with cold 10% aqueous ammonium hydroxide the washing should be continued until the filtrate is basic. Disconnection of the vacuum during each washing is recommended. The final aqueous wash should be no more basic than pH 8-9. Use of a rubber dam facilitates the filtration and washing.

5. The proton magnetic resonance spectrum of 2 exhibits the following absorptions (CDCl_3) δ : 5.42 (s, 2 H, CH_2Br), 7.65-7.91 (complex, 4 H, aromatic).

6. Triethyl phosphite was purchased from Aldrich Chemical Company, Inc.

7. The exothermic reaction usually commences after all of the solid has dissolved. It is important to allow this exothermic reaction, which lasts about 5 min, to run its course without cooling, since premature cooling results in lower yields of impure product which may be difficult to purify.

8. Use of impure N-bromomethylphthalimide or incomplete reaction may lead to the formation of a gummy or mushy residue at this stage, and the addition of petroleum ether (bp 60-68°C) might facilitate crystallization. Alternatively, the crude product may be purified by dissolving it in a minimum volume of anhydrous ether, addition of petroleum ether (bp 60-68°C) until the solution turns cloudy, and then cooling. Scratching may be necessary to induce crystallization. Several crops of crystals may be collected, but the total yields thus obtained are generally lower than 80%.

9. The proton magnetic resonance spectrum of product 3 exhibits the following absorptions (CDCl₃) δ : 1.31 (t, 6 H, $J = 7$, CH₂CH₃), 3.83-4.26 (complex, 6 H, OCH₂, NCH₂P), 7.60-7.86 (complex, 4 H, aromatic).

10. Absolute ethanol was purchased from Aaper Alcohol and Chemical Company and used without further purification. Slight heating may be required to effect solution.

11. Hydrazine, 95%, was purchased from Eastman Organic Chemicals.

12. Since it may undergo reaction with benzaldehyde in the subsequent step to give benzaldehyde azine, it is advisable to remove the last traces of hydrazine by rotating the flask under reduced pressure. The submitters used an oscillating motor which operates on compressed air or vacuum and is commonly employed with Kugelrohr distilling units. One such motor is available from the Aldrich Chemical Company, Inc.

13. Diethyl aminomethylphosphonate undergoes decomposition upon attempted distillation, but no deterioration of the product was observed if these operations were executed at temperatures not exceeding 30°C.

14. The proton magnetic resonance spectrum of crude 4 exhibits the following absorptions (CDCl_3) δ : 1.31 (t, 6 H, $J = 7$, CH_2CH_3), 2.68 (br s, 2 H, NH_2), 3.00 (d, 2 H, $J = 10$, PCH_2N), 3.95-4.27 (complex, 4 H, aromatic).

15. The proton magnetic resonance spectrum of 5 exhibits the following absorptions (CDCl_3) δ : 1.32 (t, 6 H, $J = 7$, CH_2CH_3), 3.85-4.24 (complex, 6 H, CH_2CH_3 , PCH_2N), 7.24-7.40 (complex, 3 H, para, meta Ph CH), 7.64-7.75 (complex, 2 H, ortho Ph CH), 8.25 (d, 1 H, $J = 5$, $\text{N}=\text{CHPh}$). This material shows no significant tendency to deteriorate when stored under dry nitrogen at room temperature.

16. The apparatus was flame dried under a flow of dry nitrogen and then kept under a slight positive pressure of nitrogen during the reactions by maintaining a slow flow of nitrogen through a mercury bubbler.

17. Tetrahydrofuran was distilled from the potassium ketyl of benzophenone. (Caution: See *Org. Synth., Collect. Vol. 5* 1973, 976 for a warning regarding the purification of tetrahydrofuran.)

18. Butyllithium was prepared by dilution of 90% butyllithium obtained from Lithium Corporation of America with purified hexane or petroleum ether (bp 60-68°C) (Note 19). The normality was determined prior to use by titration according to the method of Watson and Eastman.⁹

19. Hexane was purified by preliminary stirring over concentrated sulfuric acid and then anhydrous potassium carbonate followed by distillation. The hexane thus obtained was then distilled from sodium wire.

20. The proton magnetic resonance spectrum of 6 exhibits the following absorptions (CDCl_3) δ : 2.52 (br s, 3 H, $\text{C}-\text{CH}_3$), 7.20-7.65 (complex, 9 H, aromatic), 7.86 (m, 2 H, aromatic), 8.33 (br s, 1 H, $\text{N}=\text{CHPh}$).

21. Allyl bromide was purchased from Aldrich Chemical Company, Inc., and distilled from pulverized calcium hydride and filtered through basic alumina (10 g) immediately prior to use.

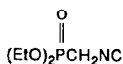
22. The proton magnetic resonance spectrum of **7** exhibits the following absorptions (CDCl_3) δ : 1.32 (s, 3 H, CCH_3), 2.49 (d, 2 H, $J = 7$, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.88 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.45 (m, 1 H, $\text{CH}=\text{CH}_2$), 7.14 (m, 5 H, aromatic), 9.33 (s, 1 H, CHO).

3. Discussion

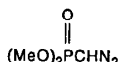
The procedure in the present reaction sequence for the preparation of N-bromomethylphthalimide (**2**) is a modification of that reported by Pucher and Johnson.² N-Bromomethylphthalimide has also been prepared by treatment of N-hydroxymethylphthalimide with phosphorus tribromide.³ The procedures for the syntheses of the phosphonates **3** and **4** represent modifications of those described by Yamauchi and co-workers.^{3,4} Two other routes to **4** have recently been reported by Gross and co-workers.⁵ Ratcliffe and Christensen have also recorded the preparation of diethyl N-benzylideneaminomethylphosphonate (**5**) by the condensation of benzaldehyde with **4** under virtually identical conditions as detailed herein, but their route to **4** was completely different.⁶ The submitters have found that the present method for the syntheses of **2-5** gives reproducibly higher yields and is more reliable and convenient than those alternative procedures.

Diethyl N-benzylideneaminomethylphosphonate (**5**) has been previously employed as an intermediate in the synthesis of β -lactam antibiotics⁶ and as a reagent for the homologation of aldehydes and ketones via intermediate 2-azadienes.⁷ Other derivatives of dialkyl aminomethylphosphonates have also

emerged as useful synthetic reagents. For example, diethyl isocyanomethylphosphonate (**8**) may be employed for the conversion of aldehydes and ketones to



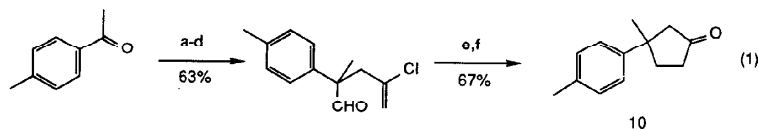
8



9

α,β -unsaturated isocyano compounds.¹⁰ Dimethyl diazomethylphosphonate (**9**)¹¹ has recently been shown to be an effective reagent for the elaboration of aldehydes or alkyl aryl ketones and diaryl ketones to alkynes¹² and for the conversion of dialkyl ketones into aldehydic enol ethers and enamines.¹³

Part D of the present procedure represents a slight modification of a general method for effecting the net replacement of both of the carbon-oxygen bonds of a carbonyl group with an acyl group and a functionalized alkyl appendage; some typical examples of the original procedure are collected in Table I.¹⁴ Moreover, when the electrophile employed for alkylation of the intermediate metallocenamine¹⁵ is properly selected, it is possible to introduce geminal substituents at the carbonyl function that are suitably functionalized for subsequent conversion either to 4,4-disubstituted cyclopentenones (eq. 1)¹⁴ or 4,4-disubstituted cyclohexenones (eq. 2).¹⁵

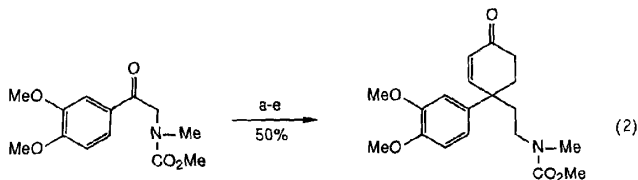


a. $\text{(EtO)}_2\text{P(=O)CHLiN=CHPh/THF/-78}^\circ\text{C} \rightarrow \text{reflux}$; b. $\text{BuLi/-78}^\circ\text{C}$;

c. $\text{CH}_2=\text{CClCH}_2\text{Cl/THF/HMPA/-78}^\circ\text{C} \rightarrow \text{reflux}$; d. H_3O^+ ; e. $\text{Hg(OAc)}_2/\text{HCO}_2\text{H/RT}$

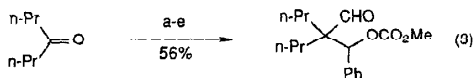
f. KOH/aq MeOH/RT

The preparation of **10** represents a formal total synthesis of α -cuparenone. An annulation related to that depicted in eq. 2, which was a key step in an



- a. $(\text{EtO})_2\text{P}(\text{O})\text{CHLiN}=\text{CHPh}/\text{THF}/-78^\circ\text{C} \rightarrow \text{reflux}$; b. $\text{BuLi}/-78^\circ\text{C}$;
 c. $\text{BrCH}_2\text{CH}_2\text{C}(\text{OCH}_2\text{CH}_2\text{O})\text{CH}_3/\text{THF}/\text{HMPA}/-78^\circ\text{C} \rightarrow \text{RT}$;
 d. $\text{H}_3\text{O}^+/\text{RT}$; e. $\text{KOH}/\text{aq MeOH}/\text{RT}$

efficient synthesis of mesembrine,¹⁶ has also been featured in total syntheses of the Amaryllidaceae alkaloids lycoramine¹⁷ and crinine.¹⁸ Finally, the intermediate metalloenamines may be utilized as the nucleophilic partners in directed aldol reactions (eq. 3), but it appears to be necessary to trap the intermediate β -oxidoimines by acylation or alkylation to avoid retro-aldolization during the hydrolysis step.¹⁴ Such a process has recently been exploited in the syntheses of the Amaryllidaceae alkaloids pretazettine and haemanthidine.¹⁹



- a. $(\text{EtO})_2\text{P}(\text{O})\text{CHLiN}=\text{CHPh}/\text{THF}/-78^\circ\text{C} \rightarrow \text{reflux}$; b. $\text{BuLi}/-78^\circ\text{C}$;
 c. PhCHO ; d. $\text{MeOCOCV}/-78^\circ\text{C} \rightarrow \text{RT}$; e. $\text{H}_3\text{O}^+/\text{RT}$

It presently appears that this methodology is well suited for the construction of quaternary carbon atoms bearing substituted alkyl appendages containing a diverse array of functionality. In large measure this is because

metalloenamines, which are the key synthetic intermediates, are highly nucleophilic and generally undergo regioselective reaction at carbon with a variety of weak and multifunctional electrophiles. Moreover, numerous functional groups may be present on the starting aldehyde or ketone, but there has been a report²⁰ which suggests that carbonyl compounds bearing potential leaving groups on the carbon adjacent to the carbonyl group may not be good substrates. While a number of individual operations are required, it is frequently possible to execute the entire sequence of reactions in a single flask. In this particular preparation the sequence may also be performed in a single vessel, but purification of product 7 by simple distillation is more difficult because of the presence of lower boiling impurities.

Table I. Geminal Acylation-Alkylation of Carbonyl Compounds

$ \begin{array}{ccc} \text{R}_1 & & \text{R}_1 \text{ CHO} \\ & \diagdown \quad \diagup & \diagdown \quad \diagup \\ & \text{C}=\text{O} & \text{C} \\ & \diagup \quad \diagdown & \diagup \quad \diagdown \\ \text{R}_2 & & \text{R}_2 \quad \text{R}_3 \end{array} $				
Entry	R ₁	R ₂	R ₃	% Overall Yield ^a
1	C ₆ H ₁₃	H	Me	34
2	o-C ₆ H ₁₁	H	Me	43
3	n-Pr	n-Pr	Me	58
4	-(CH ₂) ₅ -		CH ₂ CH=CH ₂	51
5	-(CH ₂) ₂ CH(t-Bu)(CH ₂) ₂ -		Me	63 ^b
6	-CH ₂ C(Me) ₂ CH ₂ C(Me)=CH-		Me	80
7	Ph	Me	Me	77

a. Yields are of distilled products but are not optimized.

b. As a ca. 79:21 mixture of diastereomers.

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20. For example see: Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 2533.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diethyl N-benzylideneaminomethylphosphonate: Phosphonic acid, [[(phenylmethylene)amino]methyl]-, diethyl ester (9); (50917-73-2)

2-Methyl-2-phenyl-4-pentenal: 4-Pentenal, 2-methyl-2-phenyl- (8,9); (24401-39-6)

N-Bromomethylphthalimide: Phthalimide, N-(bromomethyl)- (8); 1H-Isoindole-1,3-(2H)-dione, 2-(bromomethyl)- (9); (5332-26-3)

N-Hydroxymethylphthalimide: Phthalimide, N-(hydroxymethyl)- (8); 1H-Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)- (9); (118-29-6)

Hydrobromic acid (8,9); (10035-10-6)

Diethyl phthalimidomethylphosphonate: Phosphonic acid, (phthalimidomethyl)-, diethyl ester (8); Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]-, diethyl ester (9); (33512-26-4)

Triethyl phosphite: Phosphorous acid, triethyl ester (8,9); (122-52-1)

Hydrazine (8,9); (302-01-2)

Diethyl aminomethylphosphonate: Phosphonic acid, (aminomethyl)-, diethyl ester (9); (50917-72-1)

Benzaldehyde (8,9); (100-52-7)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Acetophenone (8); Ethanone, 1-phenyl- (9); (98-86-2)

2-Phenyl-N-(phenylmethylene)-1-propen-1-amine: 1-Propen-1-amine,

2-phenyl-N-(phenylmethylene)- (9); (64244-34-4)

Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

Phosphorous tribromide: Phosphorus bromide (8); Phosphorous tribromide (9); (7789-60-8)

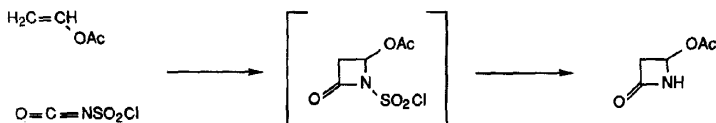
Diethyl isocyanomethylphosphonate: Phosphonic acid, (isocyanomethyl)-, diethyl ester (9); (41003-94-5)

Dimethyl diazomethylphosphonate: Phosphonic acid, (diazomethyl)-, dimethyl ester (8,9); (27491-70-9)

4-ACETOXYAZETIDIN-2-ONE: SYNTHESIS OF A KEY BETA-LACTAM

INTERMEDIATE BY A [2 + 2] CYCLOADDITION ROUTE

(2-Azetidinone, 4-(acetyloxy)-)



Submitted by Stuart J. Mickel,¹ and modified by Chi-Nung Hsiao and Marvin J. Miller.²

Checked by Daniel A. Aguilar, John Czepiel, and Gabriel Saucy.

1. Procedure

A 500-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, rubber septum with a nitrogen source, thermometer, and a pressure-equalized dropping funnel is charged with 150 mL (140 g, 1.63 mol) of vinyl acetate (Notes 1 and 2). Stirring is initiated and the flask content is cooled in an ice-water bath to 3°C. Chlorosulfonyl isocyanate (25 mL, 40 g, 0.28 mol) (Notes 2 and 3) is added as rapidly as possible from the addition funnel while maintaining the temperature at less than 5°C. The cooling bath is removed and the temperature is allowed to rise to 10°C. At this point an exothermic reaction begins. Intermittent cooling is required as the temperature is kept at 10-15°C for 40 min. The dark red mixture is then cooled to -40°C in a dry ice-acetone bath.

A 1.0-L, three-necked flask equipped with a thermometer, mechanical stirrer, and a septum cap is charged with a mixture of 67 g (0.80 mol) of sodium bicarbonate, 71.5 g (0.69 mol) of sodium bisulfite, and 200 mL of water. This mixture is cooled in a dry ice-acetone bath to -20°C with vigorous stirring. Immediately (Note 4) the reaction mixture is added dropwise via cannula at a rate such that the temperature remains at -10°C . This addition takes 30-40 min. When approximately half of the reaction solution has been added, an additional 35.7 g (0.34 mol) of sodium bisulfite is added to the aqueous quench mixture. After the addition is complete, the mixture is stirred for an additional 40 min at -10°C . The light yellow mixture (pH 7) is extracted with three 500-mL portions of chloroform (Note 5). The combined extracts are dried over magnesium sulfate and concentrated on a rotary evaporator at $40^{\circ}\text{C}/70$ mm (Note 6). Final solvent removal with a vacuum pump gives a two-phase, oily mixture. The mixture is stirred with three 100-mL portions of hexane, and the hexane extracts are decanted (Note 7) and discarded. Removal of the final traces of solvent with a vacuum pump gives 16.1-22.8 g (44-62% yield based on chlorosulfonyl isocyanate) of a light orange oil which slowly solidifies upon standing at -20°C . The resulting solid melts at 34°C (Note 8).

2. Notes

1. Commercial vinyl acetate (Aldrich Chemical Company, Inc.) was used directly without purification. The checkers observed that distilled vinyl acetate afforded slightly higher yields and improved product purity (Note 7).

2. The volume of reagents used was determined by cannulation into the graduated addition funnel before charging into the reaction flask.

3. Aldrich Chemical Company, Inc. chlorosulfonyl isocyanate was used directly without purification.

4. The mixture tended to freeze if allowed to stand at -20°C .

5. Filtration of the mixture through sintered glass aided in breaking emulsions.

6. Room temperature is even more satisfactory although the concentration takes longer. Heat leads to decomposition of the product.

7. The hexane-soluble impurity is believed to originate in the vinyl acetate. This purification may not be necessary in all cases.

8. The material prepared by this route contains a trace of a yellow impurity (vinyl acetate polymer?). However, the impurity is not detected in the ^1H NMR, ^{13}C NMR, or mass spectrum of the product. Very careful column chromatography is required to remove the color and in the hands of the submitters 4-acetoxiazetidin-2-one,⁴ prepared by the above method, is adequate for any further manipulation. High vacuum distillation may be employed to obtain a colorless sample (bp $80-82^{\circ}\text{C}/10^{-3}$ mm); however, extensive losses occur. The spectra are as follows: IR (CHCl_3) cm^{-1} : 3350 (NH), 1790 (beta-lactam C=O), 1730 (acetate C=O); ^1H NMR (CDCl_3) δ : 2.03 (s, 3 H, OCOCH_3), 3.00 (d of d, 1 H, $J_{3b-3} = 15.0$, $J_{3b-4} = 1.5$), 3.28 (d of d, 1 H, $J_{3a-3b} = 15.0$, $J_{3a-4} = 4.6$, H_{3a}), 5.81 (d of d, 1 H, $J_{4-3a} = 4.6$, $J_{4-3b} = 1.6$), 7.4-7.1 (br, 1 H, NH); ^{13}C NMR (CDCl_3) δ (off resonance multiplicity, assignment): 45.0 (t, C3), 73.2 (d, C4), 166.4 (s, C2).

Thin layer chromatographic analysis of 4-acetoxiazetidin-2-one was carried out on E. Merck Silica gel F254 plates by elution with ethyl acetate. The hexane-soluble impurity (R_f 0.67) was detected by shortwave UV. 4-Acetoxiazetidin-2-one (R_f 0.38) was detected by exposure of the plate for 5 min to chlorine gas followed by spraying with TDM solution (Note 9) and heating with a hot air gun.

9. TDM spray solution was prepared as follows: Solution A: 2.5 g of 4,4'-tetramethyldiaminodiphenylmethane (TDM) was dissolved in 10 mL of glacial acetic acid and diluted with 50 mL of H_2O . Solution B: 5 g of potassium iodide was dissolved in 100 mL of H_2O . Solution C: 0.3 g of ninhydrin was dissolved in 90 mL of H_2O diluted with 10 mL of glacial acetic acid. Solutions A and B and 1.5 mL of solution C were mixed and stored in a brown bottle.

3. Discussion

Within the current synthetic effort in beta-lactam chemistry, 4-acetoxazetidin-2-one and its derivatives play an important role in the total synthesis of many conventional beta-lactams and their analogues.³⁻⁶ There is therefore a requirement for a simple large-scale preparative method for this key intermediate. This synthesis is a modification of that reported by Clauss et al.⁷

1. School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, England. We thank the SERC for support.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

4-Acetoxyazetidin-2-one: 2-Azetidinone, 4-hydroxy-acetate (ester) (8);

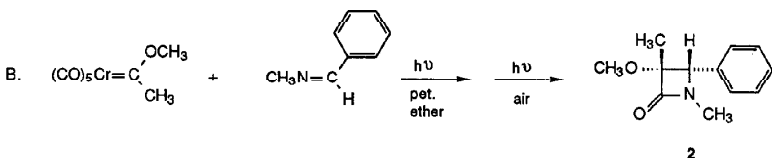
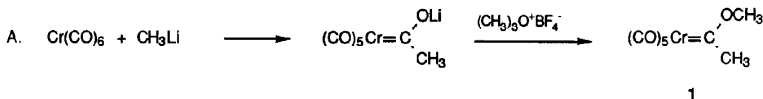
2-Azetidinone, 4-(acetyloxy)- (9); (28562-53-0)

Vinyl acetate: Acetic acid vinyl ester (8); Acetic acid ethenyl ester (9);
(108-05-4)

Chlorosulfonyl isocyanate: Sulfuryl chloride isocyanate (9); (1189-71-5)

1,3-DIMETHYL-3-METHOXY-4-PHENYLAZETIDINONE

(2-Azetidinone, 3-methoxy-1,3-dimethyl-4-phenyl-)



Submitted by Louis S. Hegedus, Michael A. McGuire, and Lisa M. Schultze.¹

Checked by Ming Chang P. Yeh and Martin F. Semmelhack.

1. Procedure

A. [(Methyl)(methoxy)carbene]pentacarbonyl chromium(0).² A 1-L, two-necked, round-bottomed flask equipped with magnetic stirring bar, 100-mL addition funnel, reflux condenser, and gas inlet is charged with 18.7 g (0.085 mol) of chromium hexacarbonyl (Note 1). The apparatus is evacuated (oil pump) and filled with argon (four cycles), and a positive pressure is maintained with an argon-filled balloon on a T-tube. Dry diethyl ether (500 mL) is transferred via cannula into the flask and stirring is commenced. The addition funnel is charged with 60 mL (1.42 M in ether, 0.085 mol) of methyllithium via cannula and rapid dropwise addition is begun. The methyllithium is added over a 15-min period during which time the solution turns from bright yellow to dark brown. The solution is heated at reflux for

approximately 1.5 hr. After the solution is cooled, the solvent is removed by rotary evaporation. The dark brown residual solid is taken up in 80 mL of water (in air), and 13.0 g (0.088 mol) of trimethyloxonium tetrafluoroborate (Note 2) is added over a 30-min period with stirring (Note 3). The mixture is extracted several times with 200-mL portions of cold pentane (Note 4). The combined pentane layers are dried over anhydrous magnesium sulfate and filtered through a bed of Celite. The solution is concentrated by rotary evaporation to approximately 60 mL and is cooled to -20°C under argon. After 1 hr the resulting bright yellow crystals (17.6 g, 83%) are collected and dried at 25°C under reduced pressure for 10 min (Note 5).

B. 1,3-Dimethyl-3-methoxy-4-phenylazetidinone. A 250-mL Pyrex Erlenmeyer flask is charged with 1.25 g (5.0 mmol) of [(methyl)(methoxy)carbene]penta-carbonyl chromium(0)]. The flask is fitted with a rubber septum, evacuated and filled with argon (four cycles). Dry petroleum ether (175 mL) is transferred via cannula into the flask to produce a dark yellow solution. The solution is charged with 0.59 g (5.0 mmol) of N-methylbenzylideneimine (Note 6). The flask is irradiated with six 20-Watt Vitalites (Note 7). The solution turns brown and heterogeneous within an hour. After 3 days (Note 8) the solution is filtered through a bed of Celite, the precipitate is washed with dry petroleum ether, and the now lighter yellow solution is sealed in a flask, degassed, and irradiated as before. After 5 days of further irradiation, the mixture is filtered and the filtrate is exposed to air and irradiated again until a colorless solution is obtained (approx. 1 day). Filtration through a bed of Celite and removal of solvent by rotary evaporation affords colorless crystals of essentially pure β -lactam 2. Recrystallization from hexane gives 0.67-0.76 g (65-74% yield), mp $76-77^{\circ}\text{C}$ (Note 9).

2. Notes

1. Chromium hexacarbonyl was obtained by the checkers from Pressure Chemical Company, Pittsburgh, PA, and used without purification. It can be weighed in air as it is relatively non-volatile and air-stable. The usual precautions appropriate for a potentially toxic metal carbonyl should be employed, but the low volatility makes handling relatively easy.

2. The checkers obtained trimethyloxonium tetrafluoroborate from Alfa Products, Morton/Thiokol, Inc..

3. Meerwein's reagent was added until the pH of the solution was slightly acidic.

4. The carbene complex is slightly air sensitive in solution. The pentane was cooled to 0°C and nitrogen was bubbled through the solvent before use.

5. Longer drying resulted in loss of carbene complex by sublimation. The carbene complex was stored under argon at -20°C. The pure product shows ^1H NMR (CDCl_3) δ : 4.60 (s, 3 H, OCH_3) and 2.90 (s, 3 H, CH_3).

6. The checkers obtained N-methylbenzylideneimine from Aldrich Chemical Company, Inc., and used it without purification. It was added as a neat liquid, via syringe.

7. Vitalites were obtained by the checkers from a local hardware store. They were arranged horizontally, in banks of two in a way to provide maximum illumination of the flask. Aluminum foil was used generously around the outside of the lights in order to minimize light loss.

8. Precipitate forms and reduces light intensity in the solution. The complete conversion of reactants can be accelerated by more frequent filtration and by using sunlight in place of the Vitalites. The submitters

were successful using the Vitalites with five filtrations over a 72-hr period. The checkers found that the reaction was incomplete under these conditions and the β -lactam must be purified by chromatography (silica gel column, elution with 1:1 ethyl acetate:hexane) in order to remove residual benzaldehyde and other minor impurities.

9. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 1.60 (s, 3 H, CH_3); 2.80 (s, 3 H, NCH_3); 3.03 (s, 3 H, OCH_3); 4.35 (s, 1 H, CH); 7.28 (s, 5 H, ArH); IR (CHCl_3) cm^{-1} : 1750.

3. Discussion

The procedure described is an efficient conversion of imines to β -lactams.³ It is very general, and imines such as thiazolines, benzothiazines, dihydroisoquinoline, and quinoline itself, as well as simple aldehyde and ketone imines are converted to β -lactams in fair to good yield. The reaction is stereospecific, producing only one diastereoisomer of the β -lactam. The chromium carbene complex is easy to prepare on a large scale, to store, and to handle, since it is air stable as a solid. The β -lactam forming-reaction proceeds under very mild conditions and requires only the most simple glassware and either sunlight or commercially available fluorescent tubes which duplicate the spectrum of sunlight, (e.g., Vitalite). Product isolation consists of simple filtration and solvent removal. The procedure produces β -lactams containing heteroatom substituents at the 3-position. It is complementary or superior to existing methods for the conversion of imines to β -lactams involving ketenes,⁴ acid chlorides and base,⁵ or ketene silyl acetals.⁶

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,3-Dimethyl-3-methoxy-4-phenylazetidinone: 2-Azetidinone, 3-methoxy-1,3-dimethyl-4-phenyl- (11); (82918-98-7)

[(Methyl)(methoxy)carbene]pentacarbonyl chromium(0): Chromium, pentacarbonyl(1-methoxyethylidene)-, (8); Chromium, pentacarbonyl(1-methoxyethylidene)-, (OC-6-21)-, (9); (20540-69-6)

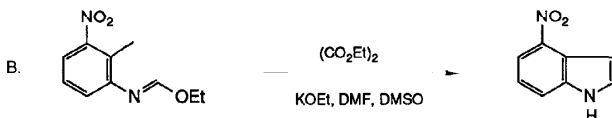
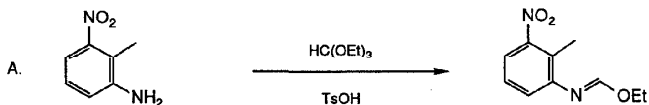
Chromium hexacarbonyl: Chromium carbonyl (8); Chromium carbonyl (OC-6-11)- (9); (13007-92-6)

Methyl lithium: Lithium, methyl- (8,9); (917-54-4)

Trimethyloxonium tetrafluoroborate: Oxonium, trimethyl-, tetrafluoroborate (1-) (8,9); (420-37-1)

N-Methylbenzylideneimine: Methylamine, N-benzylidene- (8); Methanamine, N-(phenylmethylene)- (9); (622-29-7)

4-NITROINDOLE
(Indole, 4-nitro-)



Submitted by Jan Bergman and Peter Sand.¹

Checked by Cynthia A. Smith and Andrew S. Kende.

1. Procedure

A. *Ethyl N-(2-methyl-3-nitrophenyl)formimidate.* A 1-L, one-necked, round-bottomed flask, fitted with a Claisen condenser protected from moisture with a drying tube, is charged with 200 g (1.35 mol) of freshly distilled triethyl orthoformate, 1 g of p-toluenesulfonic acid and 152 g (1 mol) of 2-methyl-3-nitroaniline (Notes 1 and 2). The solution is heated to 120°C and all of the ethanol formed is continuously distilled off during ca. 1 hr. Fractional vacuum distillation of the residue gives at 156-158°C/6 mm, the imidate ester, 184 g (88%), as a light yellow, solidifying oil, mp 57-58°C.

B. 4-Nitroindole. To a solution of 22 g (0.15 mol) of diethyl oxalate in 50 mL of dry dimethylformamide in a 200-mL beaker is added, under cooling, 11 g (0.13 mol) of potassium ethoxide with vigorous stirring (Notes 3 and 4). The solution is immediately (within a few seconds) poured into a 250-mL flask containing a solution of 20.8 g (0.10 mol) of ethyl N-(2-methyl-3-nitrophenyl)formimidate in 75 mL of dry dimethyl sulfoxide (Note 5). The resulting deep red solution is stirred for 1 hr at ca. 40°C (Notes 6 and 7). The solution is then transferred into a 1-L beaker and water is added under stirring at a rate which gives smooth precipitation of 4-nitroindole. The product is filtered off and dried giving 16.3 g (ca. 100%) of a brownish-yellow solid, mp 195-201°C (subl.), which is sublimed at 170°C/0.5 mm giving 11.5 g (71%) of yellow crystals, mp 204-205°C (subl.) (Note 8).

2. Notes

1. 2-Methyl-3-nitroaniline and triethyl orthoformate were purchased from Fluka AG.

2. Trimethyl orthoformate is not suitable for this preparation because of sideproduct formation.

3. Diethyl oxalate was purchased from Merck and Company, Inc., and was used without further purification. Potassium ethoxide was purchased from Alfa Products, Morton/Thiokol Inc. or preferably was prepared from potassium metal and absolute ethanol.

4. The diethyl oxalate/potassium ethoxide complex can also be prepared by adding the oxalic ester to an ethanolic solution of potassium ethoxide and evaporating the solvent. However, this complex is less active and is difficult to store.

5. Dimethyl sulfoxide (DMSO) prevents precipitation of intermediate salts, which can also be achieved by using a larger volume of dimethylformamide (DMF) (ca. 200 mL). Attempts to prepare the diethyl oxalate/potassium ethoxide complex in DMSO have not been successful (i.e., it is not active).

6. At elevated temperatures (e.g., above 40°C) by-products are formed.

7. The reaction can be monitored by TLC (CH_2Cl_2). The spots were developed with an ethanolic solution of p-dimethylaminobenzaldehyde/HCl. The product gave a bright red spot at R_f 0.5 and the imidate ester gave a yellow spot at R_f 0.6. Addition of small portions of diethyl oxalate/potassium ethoxide complex was continued if the starting material was not consumed after the initial reaction period.

8. Crude 4-nitroindole can also be purified by recrystallization from methanol, ethanol, or acetonitrile giving brownish-yellow crystals, mp 204-206°C.

3. Discussion

This procedure illustrates the synthesis of 4-nitroindoles; the present method can easily be extended to the 2-alkyl derivatives (using other ortho esters), 5-, 6- and/or 7-substituted derivatives and 1-alkyl derivatives (from the corresponding N-alkylanilides).^{2,3} Other published preparations of 4-nitroindole (e.g., ref. 4) are of no practical value.

The mechanism of the formation of 4-nitroindole parallels the Reissert indole synthesis⁵ and is discussed in references 2 and 3.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Nitroindole: Indole, 4-nitro- (9); (4769-97-5)

Triethyl orthoformate: Orthoformic acid, triethyl ester (8); Ethane, 1,1',1"-[methylidynetris(oxy)]tris- (9)- (122-51-0)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

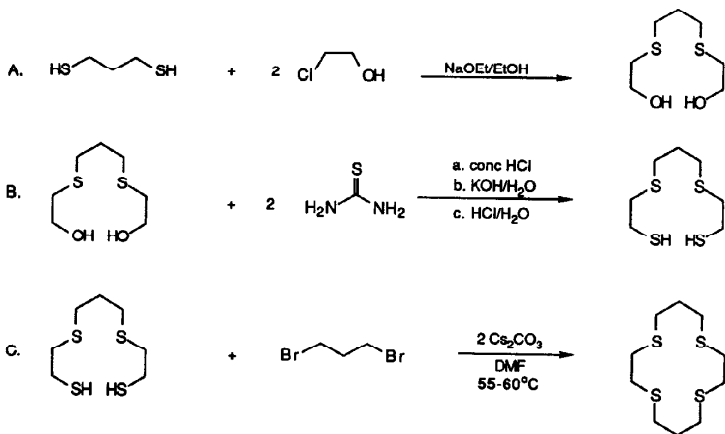
2-Methyl-3-nitroaniline: o-Toluidine, 3-nitro- (8); Benzeneamine, 2-methyl-3-nitro- (9); (603-83-8)

Diethyl oxalate: Oxalic acid, diethyl ester (8); Ethanedioic acid, diethyl ester (9); (95-92-1)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5).

SYNTHESIS OF MACROCYCLIC SULFIDES USING CESIUM THIOLATES:

1,4,8,11-TETRATHIACYCLOTETRADECANE



Submitted by J. Buter and Richard M. Kellogg.¹

Checked by Joseph M. Salvino and Bruce E. Smart.

1. Procedure

A. *3,7-Dithianonane-1,9-diol*.² A 500-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, a reflux condenser attached to a nitrogen inlet, and a pressure-equalizing dropping funnel. The flask is flushed with nitrogen and charged with 250 mL of absolute ethanol. The ethanol is stirred and 5.75 g (0.25 mol) of sodium metal is cautiously added. After the sodium dissolves, the solution is warmed to 45-50°C and 13.5 g (0.125 mol) of 1,3-propanedithiol (Note 1) is added dropwise over a period of 15 min. To the resulting solution is added dropwise 20.1 g (0.25 mol) of

2-chloroethanol (Note 1) and the mixture is refluxed for 3-4 hr. The mixture is then allowed to cool to room temperature and is filtered. The filtrate is concentrated on a rotary evaporator to a viscous liquid which is distilled to give 17.3-20.0 g (71-82%) of 3,7-dithianonane-1,9-diol, bp 200°C (1.5 mm) (Note 2).

B. *3,7-Dithianonane-1,9-dithiol*.² In a 1-L, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar are placed 35.0 g (0.178 mol) of 3,7-dithianonane-1,9-diol, 30.0 g (0.394 mol) of thiourea (Note 3), and 94 mL of concd hydrochloric acid. The mixture is stirred and refluxed for 12 hr. The resulting solution is cooled in an ice bath and 67 g (1.2 mol) of potassium hydroxide dissolved in 400 mL of water is added cautiously. The mixture is then refluxed for 3 hr. The resulting two-phase system is cooled to room temperature and the upper aqueous phase is decanted from the oily organic layer. The aqueous phase is acidified with dilute hydrochloric acid and extracted with 300 mL of ether. The ethereal extract is combined with the organic layer from the reaction mixture and this solution is dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residual liquid is distilled to give 21.4 g (53%) of 3,7-dithianonane-1,9-dithiol, bp 159-162°C (1.2 mm) (Note 4).

C. *1,4,8,11-Tetrathiacyclotetradecane*. A dry, 3-L, three-necked, round-bottomed flask is equipped with a double-necked adapter for a thermometer and the 250-mL addition funnel shown in Figure 1 (Note 5), a reflux condenser, and a mechanical stirrer with a 7-cm blade of Teflon. The entire system is kept under positive nitrogen pressure. The flask is charged with 2.2 L of N,N-dimethylformamide and 13.04 g (40 mmol) of cesium carbonate (Note 6). The mixture is stirred and heated to 55-60°C.

A solution of 9.12 g (40 mmol) of 3,7-dithianonane-1,9-dithiol and 8.08 g (40 mmol) of 1,3-dibromopropane (Note 6) in 300 mL of N,N-dimethylformamide is prepared. Half of this solution is placed in the addition funnel and added to the well-stirred suspension of cesium carbonate in N,N-dimethylformamide over a period of 6-9 hr. The reaction mixture is then charged with another 13.04 g (40 mmol) of cesium carbonate and the second half of the solution of 3,7-dithianonane-1,9-dithiol and 1,3-dibromopropane is added over a period of 6-9 hr (Note 7). After the addition is complete, the reaction mixture is allowed to cool to room temperature. The N,N-dimethylformamide is distilled off as completely as possible under reduced pressure (Note 8). The residue is taken up in 300 mL of dichloromethane and washed once with 200 mL of a saturated solution of sodium chloride. The organic layer is dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator to a light yellow crystalline mass. This is taken up in 200 mL of boiling 96% ethanol and the hot liquid is decanted. The remaining sediment is boiled with 125 mL of 96% ethanol and again decanted. The two ethanol solutions are combined and stored at 10°C overnight. The white crystalline product that separates is isolated by filtration and dried. There is obtained 6.20-6.60 g (58-62%) of 1,4,8,11-tetrathiacyclotetradecane, mp 118-119°C [lit.² mp 119-120°C] (Note 9).

2. Notes

1. 1,3-Propanedithiol and 2-chloroethanol were obtained from the Aldrich Chemical Company, Inc.

2. The submitters report obtaining 19.6-24.5 g (80-100%) of product, bp 179-181°C (0.5 mm). The product obtained by the checkers is pure by NMR and shows the following spectrum: ^1H NMR (CDCl_3) δ : 1.86 (quintet, 2 H, $J = 7$, CCH_2), 2.17 (br s, 2 H, OH), 2.65 (t, 4 H, $J = 7$, SCH_2), 2.73 (t, 4 H, $J = 6$, SCH_2), 3.73 (t, 4 H, $J = 6$, OCH_2).

3. The checkers purchased thiourea from the Aldrich Chemical Company, Inc.

4. The submitters report bp 159-161°C (0.5 mm) for the product and yields of 50-70% for reactions run with 0.1 mol of 3,7-dithianonane-1,9-diol and 0.2 mol of thiourea. The product obtained by the checkers is pure by NMR and shows the following spectrum: ^1H NMR (CDCl_3) δ : 1.63-2.07 (m, 4 H, CCH_2 , SH), 2.50-2.83 (m, 12 H, SCH_2).

5. The device illustrated in Figure 1 allows ready adjustment of addition rates without significant clogging. A is a conical ground glass receiver for the ground glass tapered end of a 7-mm diameter glass rod. The rod is turned in the tapered receiver to attain the desired rate of addition. A ratchet device attached to the top of the addition funnel holds the rod in place and measures its rotation. Outlet B is connected to a mercury bubbler and nitrogen is introduced via C.

6. The checkers obtained N,N-dimethylformamide, cesium carbonate, and 1,3-dibromopropane from the Aldrich Chemical Company, Inc. The N,N-dimethylformamide was distilled and stored over molecular sieves (4 Å) prior to use.

7. The addition rate is sufficiently slow that virtually no starting material remains. The procedure avoids the need for excessively large volumes of solvent that are normally required in high dilution reactions.

8. A Büchi rotary evaporator attached to a vacuum pump is used. A pressure of 1-2 mm is maintained and the flask is heated in a water bath to a maximum temperature of 60°C.

9. The submitters report obtaining 6.97-8.00 g (65-70%) of product, mp 118-119.5°C. The product shows the following spectral properties: IR (KBr) cm^{-1} : 2930, 1430, 1338, 1270, 1205, 1138, 692; ^1H NMR (CDCl_3) δ : 1.90 (quintet, 4 H, $J = 7$, CCH_2), 2.65 (t, 8 H, $J = 7$, SCH_2CH_2), 2.77 (s, 8 H, SCH_2).

3. Discussion

The cyclic sulfide 1,4,8,11-tetrathiacyclotetradecane has been prepared in 7.5% yield by reaction of the bis- Na^+ salt of 3,7-dithianonane-1,9-dithiol in boiling ethanol with 1,3-dibromopropane.² A marked improvement in yield by the use of cesium salts in N,N-dimethylformamide has been documented for other macrocyclic sulfides,³ as well as macrocyclic lactones,^{4,5} and amines.⁶ Moreover, the nucleophilic properties of cesium salts have been used to advantage in substitution reactions.⁷

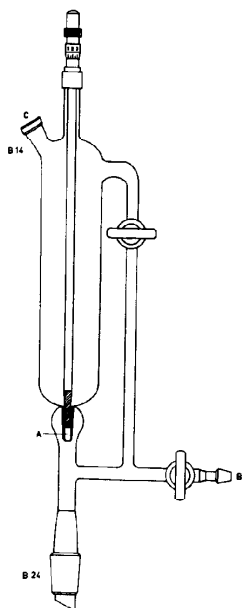
Macrocyclic sulfides, including 1,4,8,11-tetrathiacyclotetradecane, are of interest, especially as ligands for transition metal ions in a variety of different applications.⁸⁻²⁹ The methodology described here provides an efficient entry to many such macrocycles, including chiral ones that act as ligands in transition metal-catalyzed coupling reactions.²⁹

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Figure 1
Addition Funnel



Appendix

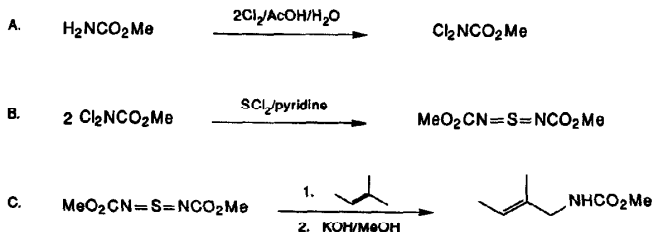
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 1,4,8,11-Tetrathiacyclotetradecane (8,9); (24194-61-4)
- 1,3-Propanedithiol (8,9); (109-80-8)
- 2-Chloroethanol (8); Ethanol, 2-chloro- (9); (107-07-3)
- 3,7-Dithianonane-1,9-diol: Ethanol, 2,2'-(trimethylenedithiol)di- (8,9); Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis- (10); (16260-48-3)
- 3,7-Dithianonane-1,9-dithiol: Ethanethiol, 2,2'-(trimethylenedithio)di- (8); Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis- (9); (25676-62-4)
- Thiourea: Urea, thio- (8); Thiourea (9); (62-56-6)
- N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)
- Cesium carbonate: Carbonic acid, dicesium salt (8,9); (534-17-8)
- 1,3-Dibromopropane: Propane, 1,3-dibromo- (8,9); (109-64-8)

ALLYLCARBAMATES BY THE AZA-ENE REACTION:

METHYL N-(2-METHYL-2-BUTENYL)CARBAMATE

(Carbamic acid, (2-methyl-2-butenyl)-, methyl ester)



Submitted by Günter Kresze, Hans Braxmeier, and Heribert Münsterer.¹

Checked by N. Laxma Reddy and Ian Fleming.

1. Procedure

Caution! All three parts of this preparation should be performed in a well-ventilated hood. The reagents and the products of parts A and B are toxic and unpleasant substances.

A. *Methyl N,N-dichlorocarbamate.* A 2-L. two-necked, round-bottomed flask equipped with a magnetic stirrer, gas inlet and gas outlet is charged with 84 g (1.1 mol) of methyl carbamate, 210 g (2.6 mol) of sodium acetate, 21 g (0.35 mol) of glacial acetic acid and 400 mL of water and cooled to -10° to -15°C (Note 1). About 175 g (2.5 mol) of chlorine is condensed in a calibrated Schlenk tube (Note 2) cooled with dry ice/methanol. The cooling bath is replaced by an ice-water bath (Note 3) and chlorine is passed slowly

(Note 4) (over 2 hr, Note 5) at a constant rate into the solution, which is vigorously stirred with a magnetic stirrer. The mixture is transferred to a separatory funnel and the yellow oil which settles is run off. The yellow oil is washed with three subsequent 50-mL portions of a 20% aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The crude product is then transferred to a distillation apparatus where it is kept under reduced pressure (11-15 mm) at room temperature for about 20 min. The bath temperature is slowly raised to a maximum of 60°C. The product distills at 43°C (11 mm) to give 102-118 g (63-73%, based on methyl carbamate) of a heavy yellow oil (Note 6, Note 7, Note 8).

B. N^1,N^2 -Bis(methoxycarbonyl)sulfur diimide. A 250-mL, three-necked, round-bottomed flask, equipped with a gas outlet stop-cock, a thermometer, and a pressure-equalizing dropping funnel and containing a magnetic stirrer bar is purged with dry nitrogen and charged with 53.0 g (0.37 mol) of methyl N,N-dichlorocarbamate and 0.2 mL of pyridine. The dropping funnel is filled with 20.6 g (0.2 mol) of freshly distilled sulfur dichloride (Note 9). The whole apparatus is closed and connected by way of the gas outlet to a paraffin oil-filled valve (Note 10). About 2 mL of sulfur dichloride is then added dropwise into the stirred flask. When the evolution of chlorine has started (usually after about 5 min) (Note 11), the remainder of the sulfur dichloride is added at such a rate that 3-5 bubbles of chlorine per second are evolved (Note 12), without allowing the temperature of the reaction mixture to exceed 35°C for more than short intervals. The addition takes 1.5 to 2 hr. After the addition is completed and the evolution of gas has slowed down significantly, volatile materials are removed by stirring the mixture at 60°C under reduced pressure (11-15 mm) for about 10 min (Note 13). Further removal is accomplished at room temperature at 0.01-0.05 mm for approximately 1 hr.

The product (33.0-35.0 g), a moisture-sensitive, viscous, yellow oil, is used directly without further purification (Note 14).

C. *Methyl N-(2-methyl-2-butenyl)carbamate*. A 250-mL, two-necked flask, equipped with a gas-outlet stop-cock and a pressure-equalizing dropping funnel, and containing a magnetic stirrer bar, is flushed with dry nitrogen and charged with a solution of N^1, N^2 -bis(methoxycarbonyl)sulfur diimide from Part B in 30 mL of dry chloroform. The solution is cooled with ice water, and 14.1 g (0.20 mol) of 2-methyl-2-butene is slowly dropped in with stirring over 1 hr. After the completion of the addition, the reaction mixture is stirred for another 10 hr at room temperature. The funnel is replaced by a distillation unit and most of the solvent is removed (11-15 mm, bath temperature 30°C). To the residue are added 240 mL of a 10% solution of potassium hydroxide in methanol and about 10 mL of water. The mixture is stirred for 3 hr at room temperature, and any precipitate is filtered off (Note 15). The residue is washed with 50 mL of methanol, and the filtrate, a red solution, is concentrated at 40°C (11-15 mm). The residue is taken up in 450 mL of ether and washed with four 100-mL portions of water. The ethereal layer is dried with anhydrous magnesium sulfate and treated with charcoal until the color has changed from red to yellow, whereupon the solvent is removed under reduced pressure. The resultant oil is distilled at 70-75°C (3 mm), 62-64°C (0.2 mm) to give the colorless product, yield 10.7-13.7 g (43-52%, based on N,N-dichlorocarbamate) (Notes 16, 17).

2. Notes

1. The solution of methyl carbamate, sodium acetate and acetic acid is best prepared at room temperature. Upon cooling small amounts of precipitate form, but this precipitate dissolves again during the reaction.

2. An amount of 175 g of condensed chlorine corresponds to a volume of about 115 mL. A dry ice-acetone condenser is fitted above the Schlenk tube.

3. A safety flask of at least 1 L should be placed between the Schlenk tube and the reaction flask.

4. To prevent chlorine from escaping before reaction has taken place, the gas inlet tube is immersed as deeply as possible into the solution.

5. To follow the rate of evaporation of chlorine, it is helpful to have calibrated the Schlenk tube.

6. The crude product should not be stored, and the distilled product is best kept protected from light at -78°C .

7. During the distillation, the product is best kept cooled in an ice-water bath.

8. The product is a powerful skin irritant. Protective gloves should be worn during the separation, and when transferring the liquid to the distillation apparatus.

9. Sulfur dichloride decomposes at its boiling point. It is best distilled at low pressure, condensing it in a cooled vessel.

10. The valve serves as a bubble counter for monitoring the evolution of gas.

11. It sometimes happens that no significant evolution of chlorine occurs. In these cases the mixture is heated to 30-40°C with a water bath, which is removed after the reaction has started. The checkers found no delay in the evolution of chlorine.

12. This evolution should not be interrupted.

13. An aspirator and a water bath may be used for this purpose. A tube filled with anhydrous calcium chloride should be placed between the aspirator and the flask.

14. The product is best stored protected from light at -78°C. Even under these conditions, it is advisable to use it up within at least 1 month.

15. Sometimes no significant amount of precipitate is formed, in which case filtration may be omitted.

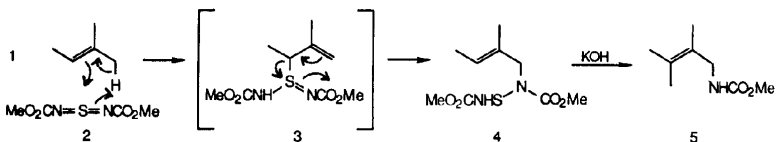
16. During distillation the receiving flask should be cooled with ice water in order to minimize losses. The product is a semisolid material at room temperature and solidifies completely when kept in a refrigerator.

17. The product has the following spectroscopic properties: IR (film) cm^{-1} : 3520 (NH), 1700 (CO) 1530; ^1H NMR (250 MHz, d_5 -pyridine) δ : 1.50 (d, 3 H, $J = 6.7$, CH_3CH), 1.59 (s, 3 H, $\text{CH}_3\text{C}=\text{}$), 3.72 (s, 3 H, CH_3O), 3.90 (d, 2 H, $J = 6$, CH_2N), 5.48 (q, 1 H, $J = 6.7$, $\text{HC}=\text{}$), 8.00 (m, 1 H, HN), with long-range splitting evident in the fine structure. It appears to be a single stereoisomer (> 97:3).

3. Discussion

The preparation of methyl N,N-dichlorocarbamate is based on work of Toglia and Swern,² and the preparation of the sulfurdithiimide is based on work of Levchenko.³ In both cases, we have modified the method and added significant details.

The synthesis of primary allylamines up to 1983 has been reviewed.⁴ Our method involves the ene reaction of various aza analogues of sulfur or selenium dioxide ($1 + 2 \rightarrow 3$), followed by [2,3]-sigmatropic rearrangement ($3 \rightarrow 4$). The use of N-tosyl activating groups, as in our earlier work⁵ and that of Sharpless,⁶⁻⁸ has the disadvantage that the N-sulfonyl group cannot easily be



removed under mild conditions, as Sharpless observed in his synthesis of gabaculine.⁸ In the present method, the methoxycarbonyl group is used in place of the sulfonyl group. It is easy to remove, but the diimide (2) is less reactive than the corresponding sulfonyl compound.⁹ Nevertheless it reacts at room temperature with a variety of alkenes, such as β -methylstyrene, 2-pentene, and cyclohexene, and more heavily substituted derivatives of these compounds.¹⁰ The urethane group can easily be hydrolyzed or reduced (lithium aluminum hydride) to give the corresponding allylamines.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl N-(2-methyl-2-butenyl)carbamate: Carbamic acid, (2-methyl-2-butenyl)-, methyl ester (11); (86766-65-6)

Methyl N,N-dichlorocarbamate: Carbamic acid, dichloro-, methyl ester (8,9); (16487-46-0)

Methyl carbamate: Carbamic acid, methyl ester (8,9); (598-55-0)

Chlorine (8,9); (7782-50-5)

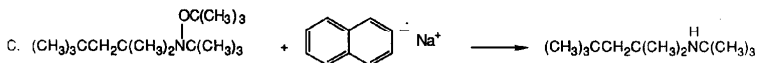
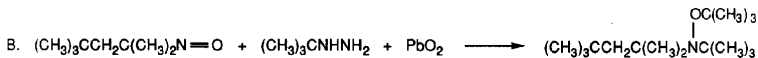
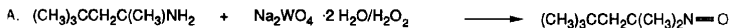
N¹,N²-Bis(methoxycarbonyl)sulfur diimide: Sulfur diimide, dicarboxy-, dimethyl ester (8,9); (16762-82-6)

Sulfur dichloride: Sulfur chloride (8,9); (10545-99-0)

Z-Methyl-2-butene: Z-Butene, 2-methyl- (8,9); (513-35-9)

tert-BUTYL-tert-OCTYLAMINE

(2-Pentanamine, N-(1,1-dimethylethyl)-2,4,4-trimethyl-)



Submitted by E. J. Corey and Andrew W. Gross.¹

Checked by Axel H. K. Paul and Clayton H. Heathcock.

1. Procedure

A. *Nitroso-tert-octane*.² To a 1-L, three-necked flask equipped with an addition funnel, a mechanical stirrer, and a thermometer are added 120 mL of methanol, 51.7 g of tert-octylamine (0.4 mol) and 90 mL of water containing 1.2 g (0.0028 mol) of the tetrasodium salt of ethylenediaminetetraacetic acid and 2.52 g (0.0076 mol) of sodium tungstate dihydrate. The solution is cooled to 15°C in an ice bath and hydrogen peroxide (361 mL of a 16% solution, 1.7 mol) (Notes 1 and 2) is added over 5 hr. The blue reaction mixture is stirred for an additional 16 hr and the product is extracted with petroleum ether (3 x 50 mL). Unreacted amine is removed by washing twice with 2 N hydrochloric acid. After the blue organic layer is washed with brine, it is dried over MgSO_4 . Petroleum ether is removed by distillation at atmospheric pressure. Continued distillation of the product affords 29.7 g of nitroso-tert-octane

(52%), bp 45-55°C, 18 mm. Upon standing, the product crystallizes as the colorless dimer, mp 63-65°C. For use in the subsequent reaction the required amount of the dimer is stirred for 1 hr in hexane to establish monomer-dimer equilibrium (Notes 3 and 4).

B. *N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine*. Into a 1-L, three-necked flask equipped with a dropping funnel, mechanical stirrer, and gas inlet tube is placed a solution of 22.8 g (0.16 mol of monomer) of nitroso-tert-octane in 500 mL of hexane. After the mixture is stirred for 1 hr, lead dioxide (132 g, 0.55 mol) (Note 5) is added. To the rapidly stirring mixture is added 48.8 g (0.55 mol) of tert-butylhydrazine (Note 6) dropwise at such a rate as to give brisk but controlled nitrogen evolution (approximately 30 min). Cooling is provided by an ice bath so as to maintain the reaction temperature between 15 and 25°C. Progress of the reaction is monitored visually by the disappearance of the blue nitroso monomer color (Note 7). After the blue color has disappeared (about 1.5 hr), the lead oxides are removed by filtration through a pad of Celite and the residue is washed with ether/hexane (1:1). The filtrate and washes are combined and the solvents are removed at reduced pressure with a rotary evaporator to give a 6:1 mixture of *N-tert-butyl-N-tert-octyl-O-tert-butylhydroxylamine* and *N-tert-octyl-O-tert-butylhydroxylamine* (Notes 8 and 9).

C. *tert-Butyl-tert-octylamine*. In a dry 500-mL, three-necked flask equipped with a mechanical stirrer, addition funnel, and nitrogen inlet are placed 25.6 g (0.20 mol) of naphthalene, 250 mL of dry tetrahydrofuran (THF), and 10.0 g (0.47 mol) of sodium pieces. The mixture is stirred at room temperature for 30 min. To the blue-green sodium naphthalenide solution is added the hydroxylamine mixture (Note 10) in 50 mL of THF over 20 min (Caution. exothermic reaction). The mixture is stirred for 2.5 hr at room

temperature (Note 11). The reaction mixture is carefully decanted from excess sodium and the excess reducing agent is cautiously quenched with isopropyl alcohol. After dilution with 150 mL of hexane, the mixture is acidified with 300 mL of ice-cold 2 N hydrochloric acid, the aqueous layer is separated, and the organic layer extracted twice more with 100-mL portions of 2 N hydrochloric acid. The combined acidic extracts are washed with 80 mL of petroleum ether (Note 12), neutralized with 4 N sodium hydroxide, and extracted with ether (3 x 100 mL). The ether extract is dried over MgSO_4 and the solvent is removed with a rotary evaporator. Distillation of the residue gives a small forerun, followed by 18-19 g of tert-butyl-tert-octylamine, bp 79°C (17 mm). The yield is 60-64% based on nitroso-tert-octane (Note 13).

2. Notes

1. Mallinckrodt 30% H_2O_2 was diluted with water to give a solution of 16% H_2O_2 in water.

2. Although it is used in excess, the amount of H_2O_2 used seems to be critical. The checkers found that the use of 2.1 mol of H_2O_2 results in considerable over-oxidation to nitro-tert-octane, resulting in a yield of nitroso-tert-octane of only 40%.

3. Nitroso-tert-octane may also be prepared by oxidation of tert-octylamine with peracetic acid in ethyl acetate, obtained by the submitters from the Union Carbide Corporation.⁴ To a 1-L, three-necked flask equipped with a mechanical stirrer and an addition funnel are added 51.7 g of tert-octylamine (0.4 mol), 50 mL of water, and 50 mL of ethyl acetate. The flask is placed in an ice bath and the contents are stirred until the temperature reaches $0-5^\circ\text{C}$. A solution of peracetic acid in ethyl acetate (3.15 M

solution, 51 mL, 0.16 mol) is added dropwise over a period of 30 min. The blue reaction mixture is stirred at 0°C until the absence of peroxy acid is indicated by starch-iodide test paper. The reaction mixture is transferred to a separatory funnel and diluted with 200 mL of hexane. Unreacted tert-octylamine is removed by washing with 4 N hydrochloric acid. The aqueous washes are backwashed until colorless with 50-mL portions of hexane. The combined, blue organic fractions are dried over sodium sulfate and used directly in the next step. When the nitroso compound is prepared in this manner, isolation is unnecessary. The checkers did not employ this procedure because the peracetic acid/ethyl acetate solution is not commercially available.

4. Care should be taken in distilling the nitroso compound because it is thermally unstable; its half-life is less than 5 min at 150°C.²

5. If technical-grade lead dioxide (Fisher Scientific Company) is used a somewhat greater amount must be added to compensate for the decreased Pb(IV) content.

6. tert-Butylhydrazine is conveniently liberated from its hydrochloride (Aldrich Chemical Company, Inc.) by distillation from 40% KOH (bp 104-107°C). The distillate consists of a mixture of tert-butylhydrazine and water. Upon addition of several grams of KOH pellets, the distillate separates into two layers. The upper layer, consisting of slightly wet tert-butylhydrazine is dried over KOH pellets.

7. Additional lead dioxide and/or tert-butylhydrazine may be necessary to complete the reaction.

8. The spectral properties are as follows: N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine ¹H NMR (CDCl₃) δ: 1.00 (s, 9 H), 1.26 (s, 12 H), 1.30 (s, 3 H), 1.31 (s, 9 H), 1.76 (s, 2 H); N-tert-octyl-O-tert-

butylhydroxylamine ^1H NMR (CDCl_3) δ : 1.01 (s, 9 H), 1.12 (s, 6 H), 1.15 (s, 9 H), 1.40 (s, 2 H), 4.44 (s, 1 H).

9. The trisubstituted hydroxylamine is sensitive to both acid and heat.

10. The yield of product is greatly reduced if the hydroxylamine mixture is not rigorously freed of solvent from the previous reaction.

11. The submitters report that the sodium naphthalenide color is discharged upon addition of the hydroxylamine mixture, and that completion of the reduction is indicated by reappearance of the characteristic blue-green color of the reagent. The checkers did not observe disappearance of the reagent color.

12. If the acidic solution is not extracted at this point, the final product will be contaminated with 2-3% naphthalene.

13. The ^1H NMR spectrum of tert-butyl-tert-octylamine is as follows (CDCl_3) δ : 1.02 (s, 9 H, CH_3), 1.19 (s, 9 H, CH_3), 1.24 (s, 6 H, CH_3), 1.44 (s, 2 H, CH_2).

3. Discussion

In addition to the procedure given here for the oxidation of tert-octylamine to nitroso-tert-octane,² the oxidation may be carried out with m-chloroperoxybenzoic acid³ or with a solution of peroxyacetic acid in ethyl acetate.⁴ The lead dioxide oxidation of alkylhydrazines to alkyl radicals appears to have general application. In addition to tert-butylhydrazine, various secondary alkylhydrazines (e.g., bornylhydrazine and menthylhydrazine) have been used to good effect. The reduction of tri-tert-alkylhydroxylamine to the di-tert-alkylamine has also been achieved with sodium in ammonia but the insolubility of the hydrophobic substrate makes this procedure difficult. The use of sodium naphthalenide⁵ gives higher yields and is more reproducible.

In addition to the commercially available 2,2,6,6-tetramethylpiperidine,⁶ di-tert-alkylamines have been prepared by Rathke⁷ by the copper-catalyzed coupling of acetylenic amines with acetylenic chlorides in an improvement of the procedure of Hennion.⁸ Di-tert-butylamine has been synthesized by the reaction of 2-methyl-2-nitropropane with sodium, followed by reduction.⁹

The three-step procedure described here illustrates a convenient, general route to di-tert-alkylamines. Extensive purification or isolation of intermediates is not required. The reactions are easily monitored. Only in the final step is the exclusion of air and moisture necessary. It should be noted that tert-butyl-tert-octylamine is considerably more hindered than 2,2,6,6-tetramethylpiperidine. tert-Butyl-tert-octylamine is inert to methyl iodide, while 2,2,6,6-tetramethylpiperidine gives a white precipitate of the pentamethylammonium iodide within minutes upon treatment with methyl iodide at room temperature. The extreme hindrance of this amine has been exploited in the selective deprotonation of carbon acids and in other reactions.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

tert-Butyl-tert-octylamine: 2-Pentanamine, N-(1,1-dimethylethyl)-2,4,4-trimethyl- (11); (90545-94-1)

Nitroso-tert-octane: Pentane, 2,2,4-trimethyl-4-nitroso- (8,9); (31044-98-1)

tert-Octylamine: 2-Pentanamine, 2,4,4-trimethyl- (9); (107-45-9)

Ethylenediaminetetraacetic acid, tetrasodium salt: Glycine, N,N'-1,2-ethanediyldis[N-(carboxymethyl)]-, tetrasodium salt, trihydrate (9); (67401-50-7)

Sodium tungstate dihydrate: Tungstic acid, disodium salt, dihydrate (8,9); (10213-10-2)

Hydrogen peroxide (8,9); (7722-84-1)

N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine (11): 2-Pentanamine, N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-2,4,4-trimethyl- (11); (90545-93-0)

Lead dioxide: Lead oxide (8,9); 1309-60-0)

tert-Butylhydrazine hydrochloride: Hydrazine, tert-butyl, monohydrochloride (8); Hydrazine, (1,1-dimethylethyl)-, monohydrochloride (9); (7400-27-3)

N-tert-Octyl-O-tert-butylhydroxylamine: 2-Pentanamine, N-(1,1-dimethylethoxy)-2,4,4-trimethyl- (10); (68295-32-9)

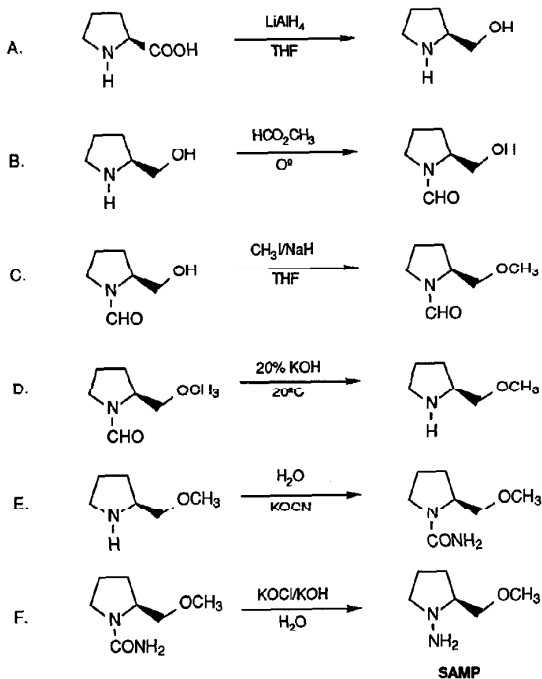
Naphthalene (8,9); (91-20-3)

Sodium (8,9); (7440-23-5)

(S)-(-)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (SAMP) AND
(R)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP),
VERSATILE CHIRAL AUXILIARIES

(1-Pyrrolidinamine, 2-(methoxymethyl)-, (S))

(1-Pyrrolidinamine, 2-(methoxymethyl)-, (R))



Submitted by Dieter Enders, Peter Fey, and Helmut Kipphardt.¹

Checked by Akira Yanagisawa and Ryoji Noyori.

1. Procedure

A. *(S)-(+)-2-Hydroxymethylpyrrolidine*. In a 4-L, three-necked, round-bottomed flask equipped with a heating mantle (Note 1), an overhead stirrer bearing a two-bladed propeller (ca. 2.5-cm diameter), an effective reflux condenser with a drying tube packed with silica gel, and a plastic stopper are placed 2.5 L of anhydrous tetrahydrofuran (THF, Note 2) and 60 g (1.56 mol) of lithium aluminum hydride (LiAlH_4 , Note 3). The suspension is heated under reflux for 15 min, the heating mantle is switched off, and 115.1 g (1 mol) of powdered (S)-proline (Note 4) is added in small portions (ca. 2 g, Note 5) to the boiling mixture at such a rate as to maintain reflux. The addition requires ca. 45 min and the contents of the flask are kept boiling for an additional 1 hr. Excess lithium aluminum hydride is then decomposed by cautiously adding a solution of 28 g of potassium hydroxide in 112 mL of water (without external heating) through a pressure-equalizing dropping funnel to the boiling mixture. Upon hydrolysis, white salts precipitate and stirring becomes difficult. After the addition is complete (ca. 25 min), the mixture is refluxed for 15 min and the hot solution is filtered by suction through a large Büchner funnel (18-cm diameter). The precipitate is pressed dry with a beaker. Any remaining prolinol is extracted from the precipitate by refluxing with 1.5 L of tetrahydrofuran for 1 hr under mechanical stirring, followed again by suction filtration. The combined filtrates are concentrated in a 2-L flask at 30°C (Note 6) under reduced pressure to yield 115-125 g of the crude hydroxymethylpyrrolidine as a pale yellow oil.

B. *(S)-()-1-Formyl-2-hydroxymethylpyrrolidine*. The 2-L flask containing the crude hydroxymethyl derivative (ca. 1 mol) is equipped with a dropping funnel and a magnetic stirring bar, and cooled to 0°C. Eighty milliliters (1.3 mol) of methyl formate (Note 7) is added over a period of 20 min and stirring is continued for 30 min at 0°C to give a green-colored solution. Excess methyl formate is evaporated at 30°C affording a dark oil, which is taken up in 600 mL of dichloromethane and dried twice by stirring over a sufficient amount of anhydrous sodium sulfate. The drying agent is removed by suction filtration through Celite (Note 8), using a large column, and the filtrate is concentrated under reduced pressure at 30°C. Any remaining traces of solvents are removed by stirring under reduced pressure using an oil pump (20°C/1 mm). This procedure takes about 2 hr and yields ca. 130 g (ca. 1 mol) of the dry, crude N-formyl compound, which is used in the next step without further purification.

C. *(S)-()-1-Formyl-2-methoxymethylpyrrolidine*. A 4-L, three-necked flask, fitted with a magnetic stirrer, reflux condenser, low temperature thermometer and a mineral oil bubbler is charged with a solution of the crude formyl derivative in 1.5 L of dry tetrahydrofuran (Note 9) and flushed with argon. The solution is cooled to -50 to -60°C (internal temperature, acetone-dry ice), the cooling bath is removed, and 81 mL (1.3 mol) of methyl iodide is added. Then 28.8 g (1.2 mol) of sodium hydride (Note 10) is introduced carefully in one portion. *CAUTION! To prevent contact of sodium hydride with the cooling medium, it is absolutely necessary to remove the cooling bath before adding the sodium hydride. In addition, argon bubbling is stopped to avoid sodium hydride dust from being blown out of the flask.* The apparatus is flushed again with argon and allowed to warm to room temperature. During this period hydrogen gas evolves and a grey solid precipitates, which causes

stirring to become difficult. At about 0°C the precipitate dissolves exothermally under strong evolution of hydrogen. The thermometer is replaced by a pressure-equalizing dropping funnel, the solution is refluxed for 15 min, and quenched by slow addition of 90 mL of 6 N hydrochloric acid, without external heating. Tetrahydrofuran is removed under reduced pressure to yield the crude O methylated compound in water.

D. *(S)-(+)-2-Methoxymethylpyrrolidine*. A solution of 180 g of potassium hydroxide in 720 mL of water is added to the crude product and the mixture is vigorously stirred under argon overnight. Saturation with potassium carbonate (500 g) causes precipitation of potassium salts, which are filtered off by suction (large Büchner funnel) and washed with ether. The filtrate is extracted with ether (3 x 300 mL) (Note 11) and the ether layer is acidified with 100 mL of 12 N hydrochloric acid under ice cooling in a hood (evolution of fumes) and extracted twice with 100 mL of water to yield an aqueous solution of the hydrochloride of 2-methoxymethylpyrrolidine (Note 12).

E. *(S)-(-)-1-Carbamoyl-2-methoxymethylpyrrolidine*. The aqueous amine hydrochloride solution is adjusted to a pH of 2.8-3.2 (Note 13) with aqueous 50% potassium hydroxide. A solution of 80 g (1 mol) of potassium cyanate (Note 14) in 140 mL of water is then added all at once at 15°C and the mixture is allowed to stir for at least 12 hr at 20°C.

F. *(S)-(-)-1-Amino-2-methoxymethylpyrrolidine (SAMP)*. A 4-L, three-necked flask containing the crude urea is cooled to -5°C (internal temperature) by means of an ice-salt bath and treated with a chilled (-5°C) solution of 168 g of potassium hydroxide in 150 mL of water. After addition of 685 mL (1.3 mol) of 1.9 N potassium hypochlorite solution (Note 15), precooled to -5°C, the temperature rises within 10 min to 30-40°C and the cooling bath is removed after the mixture reaches room temperature (Note 16). Stirring is

continued for a total of 12-15 hr. Excess potassium hypochlorite is destroyed with a freshly prepared solution of sodium bisulfite (20 g NaHSO_3 in 50 mL of H_2O) and the mixture is acidified (pH 2) with a minimum amount of 12 N hydrochloric acid (ca. 350 mL) under ice cooling. A strong evolution of carbon dioxide occurs. The mixture is allowed to stir for an additional 15 min at ambient temperature, made alkaline (pH 9) with ca. 100 mL of aqueous 50% potassium hydroxide, and saturated with potassium carbonate (500 g). Precipitated potassium salts are filtered off by suction through a large Büchner funnel and washed twice with ethanol; the filtrate is extracted with a 1:1 chloroform/ethanol mixture (1 x 800 mL and 2 x 400 mL). During extraction salt precipitation again occurs and the salts should be filtered off as mentioned above. The organic layers are collected, concentrated under reduced pressure at 30°C (Note 17), taken up in 500 mL of chloroform, and dried twice over sodium sulfate. The drying agent is removed by suction filtration through Celite and the solvent is stripped off as mentioned above to give 80-90 g of a dark oil. Immediate distillation through a 40-cm vacuum-jacketed Vigreux column (the receiver should be cooled with ice to prevent loss of substance) yields a small forerun containing 2-methoxymethylpyrrolidine, followed by SAMP as a colorless liquid, bp 42°C/1.8 mm (80°C bath temperature), $[\alpha]_D^{20}$ -79.6° (neat). Overall yields of SAMP range from 65 to 75 g (50-58%). A purity of ca. 95% was established by GLC analysis (Note 18). The optical antipode RAMP, $[\alpha]_D^{20}$ +79.8° (neat), can be prepared likewise, starting from (R)-proline (Note 19).

2. Notes

1. The heating mantle should be covered with aluminum foil to prevent contact with lithium aluminum hydride and proline.

2. *Peroxide-free* tetrahydrofuran (for precautions, see *Org. Synth., Collect. Vol. V* 1973, 976) was refluxed over potassium hydroxide pellets for 2 hr, distilled, and dried by addition of ca. 1 g of lithium aluminum hydride prior to use. *Failure to heed the precautions can result in a serious explosion!* Drying the THF over sodium-benzophenone is generally recommended for safety reasons, but this variation was not checked.

3. Lithium aluminum hydride (100%) was used as purchased from Metallgesellschaft AG, Frankfurt, Germany, or Wako Pure Chemical Industries, Ltd., Japan.

4. (S)- and (R)-proline (>99.5% ee) were obtained from Degussa AG, Hanau, Germany. The checkers used (S)-proline (guaranteed reagent) purchased from Wako Pure Chemical Industries, Ltd.

5. A convenient technique is to add the proline portion-wise with a spoon that is inserted as far as possible into the flask to prevent the proline from being blown off the spoon by hydrogen generated during the reaction. The flask is immediately stoppered after every addition.

6. The temperature of the heating bath should not exceed 30°C to avoid significant loss of product. To prevent oxidation the rotary evaporator is flushed with argon.

7. Methyl formate (reagent grade) was used as purchased from Riedel de Haen, Seelze, Germany. The checkers used the product (guaranteed reagent) of Wako Chemical Industries, Ltd.

8. Celite was supplied by Fluka AG, Buchs, Switzerland, or Manville Products Corporation, USA.

9. This time, tetrahydrofuran (Note 2) is made anhydrous by adding ca. 2 g of sodium hydride.

10. Methyl iodide was purchased from Merck-Schuchardt, Hohenbrunn, Germany, or Wako Pure Chemical Industries, Ltd., Japan. Because of its volatility and possible carcinogenicity it should be handled in a well-ventilated hood. Sodium hydride was supplied by Riedel de Haen, Seelze, Germany, or Wako Pure Chemical Industries, Ltd., Japan. In a 1-L, round-bottomed flask 50 g of 80% sodium hydride (mineral oil dispersion) is washed free of oil by stirring with pentane (4 x 300 mL). After the supernatant liquid is decanted for the fourth time, the remaining solvent is removed by evaporation (20°C/1 mm).

11. After the usual workup, the amine can be obtained pure merely by distilling through a 40-cm Vigreux column, bp 75–77°C/40 mm.

12. The ether layer contains a small amount of the starting material and is discarded.

13. The pH of the solution should be exactly calibrated by means of a pH meter in order to prevent side reactions. The use of pH paper is not recommended.

14. Potassium cyanate (technical grade) was supplied by Degussa AG, Hanau, Germany. Alternatively, sodium cyanate may be used. The checkers used the practical grade reagent purchased from Wako Pure Chemical Industries, Ltd., Japan.

15. The optimized preparation of an aqueous potassium hypochlorite solution is a modification of an Organic Syntheses procedure.² Two hundred grams of HTH [commercially available as swimming pool sanitizer from Olin Chemicals, 120 Long Ridge Road, Stamford, CT 06904, USA, ca. 68% $\text{Ca}(\text{OCl})_2$, or Nippon Soda Co., Japan, 70% $\text{Ca}(\text{OCl})_2$] is vigorously shaken with 600 mL of water (ca. 10 min), a solution (20°C) of 40 g of potassium hydroxide and 140 g of potassium carbonate in 250 mL of water is added, and shaking is continued for at least 10 min to yield a semi-fluid gel. The gel is filtered off by suction and thoroughly pressed dry to give 650-770 mL of a yellow potassium hypochlorite solution. These solutions are 1.8-2.2 M according to simple iodometric titration (see *Org. Synth.* 1976, 56, 118, Note 3).

16. Lower temperatures than those mentioned above inhibit the exothermic reaction and the reaction time is extended to approximately 24 hr. Less efficient cooling results in warming to 70-80°C, which causes decarboxylation of the intermediate carboxylate and/or simple oxidation by potassium hypochlorite.

17. If the temperature of the water bath exceeds 30°C, significant amounts of product are lost. To prevent oxidation, the rotary evaporator is flushed with argon.

18. The checkers observed contamination of the final product by ca. 4% 2-methoxymethylpyrrolidine according to 270 MHz NMR .

19. The chiral hydrazines are stable over months if stored in a refrigerator under argon. The spectra are as follows. IR (film) cm^{-1} : 3360 (NH_2), 3150, 2980, 2880, 2820, 1610, 1465, 1200, 1120, 960, 920; ^1H NMR (CDCl_3 , 90 MHz) δ : 1.4-2.1 (m, 4 H, CH_2), 2.1-2.6 (m, 2 H, CH_2N), 3.1 (m, 3 H, NH_2 , NCH), 3.3 (s, 3 H, OCH_3), 3.4 (m, 2 H, CH_2O); mass spectrum (70 eV) m/e (rel. intensity): M^+ 130.1100 (6.7%) (calcd. 130.1106); 97.07 (3.9);

86.07 (8.9); 85.07 (100.0); 83.06 (4.1); 71.06 (16.3); 68.05 (31.3); 57.04 (5.6); 56.05 (4.6); 45.03 (10.7); 43.03 (12.1); 42.04 (3.4); 41.04 (28.9); 39.02 (5.5) .

3. Discussion

The previously reported preparation of SAMP and its enantiomer RAMP involved hazardous nitrosamine intermediates.³⁻⁵ The new procedure described here circumvents this problem by N-amination via Hofmann-degradation⁶ (step F). The procedure, which required an optimization of the synthesis of the known intermediates,^{7,8} is characterized by good yields, mild conditions and readily available starting materials. The entire sequence of six steps can be performed in a week.

The enantiomerically pure hydrazines SAMP and RAMP are versatile chiral auxiliaries with a wide range of applications in asymmetric synthesis.⁹ For a detailed description of the SAMP/RAMP-hydrazone method see the following Organic Syntheses procedure.

1. Institut für Organische Chemie der Rheinischen Westfälischen Technischen Hochschule, Professor-Pirlet-Strasse 1, 5100 Aachen, Germany.
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Appendix

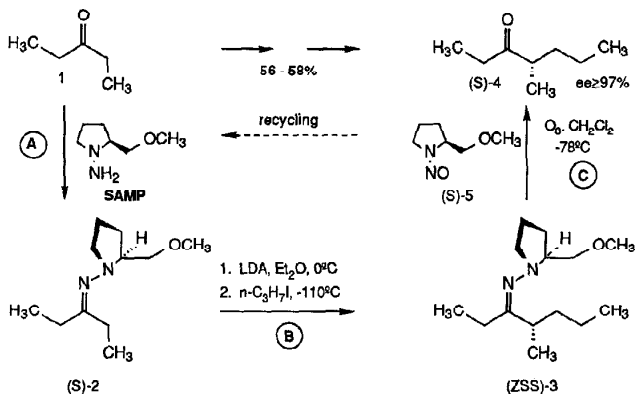
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (S)-(-)-1-Amino-2-methoxymethylpyrrolidine (SAMP): 1-Pyrrolidinamine, 2-(methoxymethyl)-, (S)- (9); (59983-39-0)
- (R)-(+)-1-Amino-2-methoxymethylpyrrolidine (RAMP): 1-Pyrrolidinamine, 2-(methoxymethyl)-, (R)- (9); (72748-99-3)
- L-Proline (8,9); (147-85-3)
- D-Proline (8,9); (344-25-2)
- (S)-(+)-2-Hydroxymethylpyrrolidine: 2-Pyrrolidinemethanol, (S)-(+)- (8,9); (23356-96-9)
- (S)-(-)-1-Formyl-2-hydroxymethylpyrrolidine: 1-Pyrrolidinecarboxaldehyde, 2-(hydroxymethyl)-, (S)- (9); (55456-46-7)
- (S)-(-)-1-Formyl-2-methoxymethylpyrrolidine: 1-Pyrrolidinecarboxaldehyde, 2-(methoxymethyl)-, (S)- (10); (63126-45-4)
- (S)-(+)-2-Methoxymethylpyrrolidine: Pyrrolidine, 2-(methoxymethyl)-, (S)- (10); (63126-47-6)

ASYMMETRIC SYNTHESIS USING THE SAMP-/RAMP-HYDRAZONE METHOD:

(S)-(+)-4-METHYL-3-HEPTANONE

(3-Heptanone, 4-methyl, (S)-)



Submitted by Dieter Enders, Helmut Kipphardt, and Peter Fey.¹

Checked by Benjamin Guzmán, Stan S. Hall, and Gabriel Saucy.

1. Procedure

A. 3-Pentanone SAMP hydrazone [(S)-2]. A 50-mL, one-necked, pear-shaped flask equipped with a 10-cm Liebig condenser, gas inlet tube, and a magnetic stirring bar is charged with 3.9 g (30 mmol) of SAMP (Note 1) and 3.79 mL (36 mmol) of 3-pentanone (Note 2) and the mixture is warmed at 60°C under argon overnight (Note 3). The crude product is diluted with 200 mL of ether in a 250-mL separatory funnel and washed with 30 mL of water. The organic layer is separated, dried over anhydrous magnesium sulfate and concentrated under

reduced pressure. Purification by short-path distillation yields 5.18 g (87%) of a colorless oil, bp 70-75°C/0.5 mm, $[\alpha]_D^{20} +297^\circ$ (benzene, $c = 1$). The SAMP-hydrazone (S)-2 should be stored in a refrigerator under argon (Note 4).

B. (S)-(+)-4-Methyl-3-heptanone SAMP hydrazone [(ZSS)-3]. A flame dried, one-necked, 250-mL flask with side arm, rubber septum and magnetic stirring bar is flushed with argon (Note 5). The flask is then cooled to 0°C and 110 mL of dry ether (Note 6) and 2.97 mL (21 mmol) of dry diisopropylamine (Note 7) are added, followed by dropwise addition of 21 mmol of butyllithium (13.1 mL of a 1.6 N solution in hexane, Note 8). Stirring is continued for 10 min and a solution of 3.96 g (20 mmol) of SAMP-hydrazone (S)-2 in 10 mL of ether is added to the stirred mixture over a period of 5 min at 0°C. Additional 2 mL of ether are used to transfer all of the hydrazone (S)-2 into the reaction flask. Stirring is continued for 4 hr at 0°C, while the lithiated hydrazone precipitates. The mixture is cooled to -110°C (pentane/liquid nitrogen bath) and kept for 15 min at this temperature. Then 2.15 mL (22 mmol) of propyl iodide (Note 9) is added dropwise, and the mixture is allowed to reach room temperature overnight. The contents of the flask are poured into a mixture of 300 mL of ether-50 mL of water in a 500-mL separatory funnel, the layers are separated, and the aqueous layer is extracted twice with 25 mL of ether. The combined organic layers are washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to yield 4.3 g (90%) of crude (ZS)-3 (Note 10).

C. (S)-(+)-4-Methyl-3-heptanone [(S)-4]. A 100-mL Schlenk tube, fitted with a gas inlet and Teflon stopcocks, is charged with 4.3 g (18 mmol) of crude (ZS)-3 dissolved in 50 mL of dichloromethane (Note 11), and cooled to -78°C (acetone/dry ice bath) under nitrogen. Dry ozone (Note 12) is passed through the yellow solution until a green-blue color appears (ca. 4 hr). The

mixture is then allowed to come to room temperature while a stream of nitrogen is bubbled through the solution to give the yellow nitrosamine (S)-5 (Note 13) and the title ketone (S)-4. The solvent is removed by distillation at 760 mm (60°C bath temperature) and the residue is transferred into a microdistillation apparatus (10-mL flask, 5-cm Vigreux column, spider, collection device, Note 14). After a small forerun (3-4 pale yellow drops), a colorless liquid distills to afford 1.6-1.7 g (56-58% overall) of ketone (S)-4; bp 63-67°C/40 mm (110-115°C bath temperature), GLC analysis 98.2%, $[\alpha]_D^{20} +21.4^\circ$ to $+21.7^\circ$ (hexane, $c = 2.2$), $[\alpha]_D^{20} +17.88^\circ$ (neat) (Note 15). To recycle the chiral auxiliary SAMP see Note 16.

2. Notes

1. (S)-1-Amino-2-methoxymethylpyrrolidine (SAMP) and RAMP are commercially available from Merck-Schuchardt (Frankfurter Strasse 250, 6100 Darmstadt or Eduard-Buchner-Strasse 14-20, 8011 Hohenbrunn, Germany) and Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The submitters prepared SAMP from (S)-proline as described in the accompanying procedure; the checkers used SAMP from Merck-Schuchardt.

2. Redistilled prior to use, 3-pentanone was obtained from Merck-Schuchardt (submitters) and Aldrich Chemical Company, Inc. (checkers).

3. The reaction was monitored by TLC. The TLC plates (SiO_2 , F₂₅₄, 0.25 mm), commercially available from Merck, Darmstadt, Germany, were eluted with ether and developed by dipping into a 10% ethanolic solution of phosphomolybdic acid (Merck) and then heating.²

4. Partial ^1H NMR spectrum (CDCl_3 , 200 MHz) δ : 1.06 (t, 3 H, J = 7.7, CH_3CH_2), 1.08 (t, 3 H, J = 7.5, CH_3CH_2), 3.34 (s, 3 H, CH_3O); IR (film) cm^{-1} : 1645.

5. This is done by alternately evacuating and filling the flask with argon three times. During the reaction a pressure of about 50 mm above atmospheric pressure is maintained using a mercury bubbler. All reagents are added via a glass syringe under rigorously anhydrous conditions. For a more detailed description of the metalation technique see reference 3.

6. The submitters used ether that had been freshly distilled from sodium and benzophenone under an argon atmosphere. The checkers used anhydrous ether directly from freshly opened 500-g containers from Fisher Scientific Company, Springfield, New Jersey. In addition, the checkers charged the reaction flask with ether using a dry graduated cylinder, flushed the system with argon and then sealed and cooled the vessel to 0°C before the sequential addition of diisopropylamine and butyllithium.

7. Diisopropylamine from BASF AG, Ludwigshafen, Germany (submitters) and Aldrich Chemical Company, Inc. (checkers) was distilled from calcium hydride, and then stored under argon and over calcium hydride until use.

8. Butyllithium was purchased from Metallgesellschaft, Frankfurt, Germany, and titrated for active alkyllithium using diphenylacetic acid as an indicator.⁴ The checkers used fresh butyllithium, 1.55 M in hexane under argon, from Aldrich Chemical Company, Inc. and omitted the titration.

9. Propyl iodide was obtained from Merck-Schuchardt, distilled over potassium carbonate and stored over copper wire under argon. *Caution: Propyl iodide is a cancer suspect agent.* The checker's source was Aldrich Chemical Company, Inc.

10. Partial ^1H NMR spectrum (CDCl_3 , 200 MHz) δ : 0.80 (t, 3 H, J = 6.9, CH_3CH_2), 1.02 (d, 3 H, J = 7.1, CH_3CH), 1.10 (t, 3 H, J = 7.5, CH_3CH_2), 3.33 (s, 3 H, CH_3O); IR (film) cm^{-1} : 1630. An ^1H -NMR experiment using the chiral shift reagent $[\text{Eu}(\text{hfc})_3]$, Aldrich] with crude 3 shows that only the (2S) isomer is present (sharp methoxy singlet). During the measurement a slow isomerization to the thermodynamically more stable (ESS) isomer takes place, but within the limit of detection of a 100-MHz spectrometer no (SR) diastereomer can be seen (diastereomeric excess $>97\%$).⁵

11. Dichloromethane was distilled over potassium carbonate prior to use.

12. *Caution! Organic ozonides are highly explosive. The reaction should be carried out in a well-ventilated hood with a shatter-proof shield. Do not grease the ground glass joints!* The submitters used a Fischer Model OZ II ozonizer from Fischer, Bad Godesberg, Germany. For detailed descriptions of a laboratory ozonizer see *Org. Synth., Collect. Vol. III* 1955, 673. The checkers used a Welsbach Model T-408 Laboratory Ozonizer, Welsbach Corp., Philadelphia, PA. The power setting was 100 volts (AC) and the oxygen pressure setting was 8 psi (0.55 kg/cm^2) to produce 2-3% ozone at a gas flow rate (rotameter) of 2 L/min. The ozone production rate was measured by passing a measured amount of ozonized gas through a 2% potassium iodide solution (neutral), acidifying with 1 M sulfuric acid, and then titrating the liberated iodine with 0.1 N sodium thiosulfate. Using these conditions, the ozonolysis required at least 4 hr, rather than the 30 min suggested by the submitters.

13. *Caution! The nitrosamine (S)-5 may be carcinogenic. All operations with (S)-5 should be performed in a well-ventilated hood, and the operator should wear disposable gloves. In order to destroy any nitrosamine traces, the glassware contaminated with (S)-5 should be immersed in a bath of HBr/acetic acid.*

14. To prevent any racemization during distillation, the apparatus is shaken with 1 mL of chlorotrimethylsilane (freshly distilled from calcium hydride), which is removed under reduced pressure. *Caution: glassware, cleaned under alkaline conditions, will lead to spontaneous racemization! The spider (3-4 arms for liquid collection) should be cooled with an ice bath. To prevent bumping, the checkers performed the distillation with a Bunsen burner rather than with a bath.*

15. The product has an optical purity of 97-98% by comparison with the reported optical rotation of $[\alpha]_D^{25} +22.1 \pm 0.4^\circ$ (hexane, $c = 1.0$) of the naturally occurring pheromone⁶ and an ee of $\geq 97\%$ by comparison with the de of $\geq 97\%$ of (ZS)-3 (Note 10); ¹H NMR (CDCl₃, 200 MHz) δ : 0.90 (t, 3 H, J = 6.7, CH₃CH₂), 1.06 (d, 3 H, J = 6.9, CH₃CH) superimposed on 1.04 (t, 3 H, J = 7.2, CH₃CH₂), 2.45 (q, 2 H, J = 7.3, CH₂CH₃); IR (film) cm⁻¹: 1710.

16. The nitrosamine (S)-5 (1.94 g, 67%) is obtained from the residue of the ketone distillation (bp 79-80°C/0.1 mm). Reduction with lithium aluminum hydride in tetrahydrofuran yields 1.47 g (49% overall) of SAMP⁷ with an $[\alpha]_D^{20} -75.46^\circ$ (neat).

3. Discussion

The title ketone (S)-4, which is 400 times more active than its optical antipode,^{6,8} is the principal alarm pheromone of the leaf cutting ant *Atta texana*. (S)-4 has also been identified as an alarm pheromone in three other ant genera of the subfamily *Myrmicinae*,^{6,9} as a component of the defensive secretion of the "daddy longleg" *Leiohnum vittatum* (Opiliones),^{10,11} and is produced by the elm bark beetles *Scolytus scolytus* (F.) and *S. multistriatus*.¹²

(S)-4 and/or its enantiomer (R)-4 have been prepared via resolution of an intermediate,⁸ starting from (R)-citronellic acid,¹³ by stoichiometric asymmetric synthesis¹⁴⁻¹⁶ (76-88% ee), and by a microbiological method.¹⁷

The three-step procedure described here, using inexpensive, commercially available starting materials and the chiral auxiliary SAMP, illustrates the synthetic utility of the "SAMP-/RAMP-hydrazone method".¹⁸ It is remarkable that the classical electrophilic substitution of a conformationally flexible, acyclic ketone **1** → (S)-4 occurs with virtually complete asymmetric induction. This demonstrates complete stereochemical control of the three critical operations: metalation, alkylation, and cleavage. Because deprotonated SAMP-/RAMP-hydrazones react with nearly the entire palette of electrophiles, this new methodology, a chiral version of the now widely used dimethylhydrazone (DMH) method,³ opens an elegant and economical entry to a great variety of important classes of compounds with good overall chemical yields and excellent diastereo- and enantioselectivities. The following stereoselective reactions may be mentioned: α-alkylations of aldehydes^{7a,19} and ketones,^{5,7a,11} diastereo- and enantioselective aldol reactions,^{7b,20,21} diastereo- and enantioselective Michael additions to form β,γ-substituted δ-keto esters,^{22,23} δ-lactones,²⁴ and various heterocycles, such as

dihydropyridines, octahydroquinolinediones and hexahydroquinolinones,²⁵ α -alkylations of β -keto esters,¹⁸ and, finally, asymmetric syntheses of α - and/or β -substituted primary amines^{18c,d} via alkylation/reductive amination of aldehydes and ketones²⁶ or nucleophilic addition to aldehyde-SAMP-/RAMP-hydrazones, followed by N-N bond cleavage.²⁷ This broad applicability is summarized in Fig. 1 and typical examples are listed in Table 1.

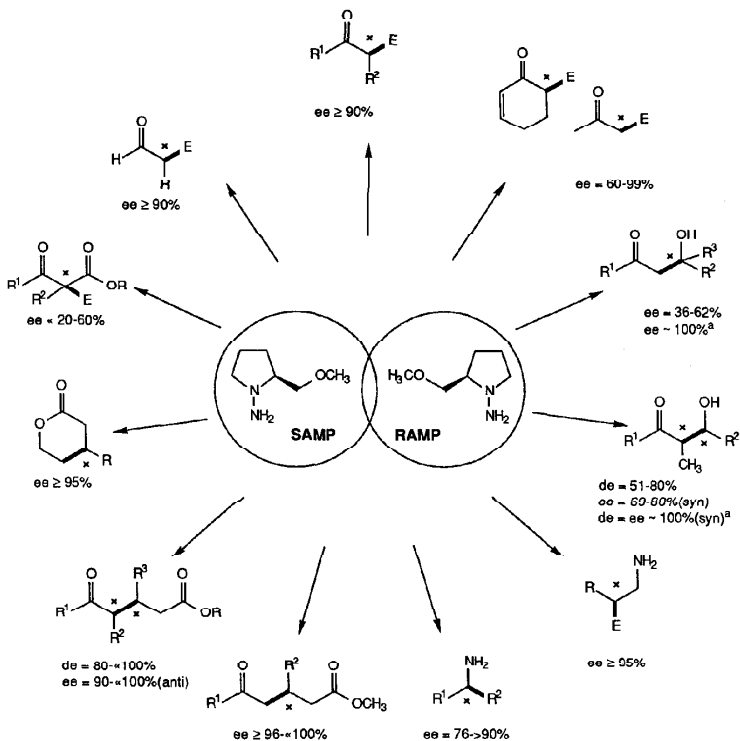
In S_F2' -front type electrophilic substitutions via SAMP-/RAMP-hydrazones the less substituted α carbon atom is regioselectively deprotonated. Under the standard reaction conditions (lithium diisopropylamide, 0°C, ether or THF) the intermediate aza enolates are formed as the $E_{CC}Z_{CN}$ species, as confirmed by spectroscopic^{19,28} and numerous trapping experiments.¹⁸ Because of the uniform diastereoface differentiation common for all asymmetric SAMP-/RAMP-hydrazone alkylations, the absolute configuration that will predominate in the final product can be predicted reliably. Furthermore, instead of changing from SAMP to the enantiomeric RAMP as chiral auxiliary, it is possible to prepare both enantiomers of target molecules in excess using SAMP, simply by changing the building blocks used as nucleophile and electrophile. This opposite enantioselectivity through synthon control is demonstrated in the cases of 2-methylbutanal, 2-methyloctanal, and 2-methyl-1-octanamine (see Table 1).

Another advantage of SAMP-/RAMP-hydrazones is the facile determination of the asymmetric induction by downfield shifting of the SAMP- or RAMP-hydrazone methoxy singlet [LIS-technique, $Eu(fod)_3$].

Besides the oxidative cleavage by ozonolysis, the optically active carbonyl compounds can be alternatively obtained by acidic hydrolysis of the corresponding SAMP-/RAMP-hydrazone methiodides in a two-phase system.^{5b,7a}

The chiral auxiliary SAMP or RAMP may be recycled by lithium aluminum hydride-reduction of the nitrosamine (S)-5 formed during ozonolysis. Other very successful applications of the SAMP-/RAMP-hydrazone method in natural product synthesis have recently been reported by Nicolaou, et al. [ionophore antibiotic X-14547A (indanomycine)];²⁹ Pennanen (eremophilanolide, sesquiterpene);³⁰ Enders, et al. (defensive substance of "daddy longlegs");¹¹ Mori, et al. (serricornin, cigarette beetle pheromone);³¹ and Bestmann, et al. (pheromone analogues).³² Finally, it should be mentioned that the chiral auxiliaries SAMP and RAMP may also be used in the resolution of aldehydes³³ and ketones,³⁴ and in the NMR spectroscopic determination of % ee of chiral aldehydes.³⁵

Figure 1. Optically Active Carbonyl Compounds and Amines



^aAfter crystallization

Table I. Optically Active Carbonyl Compounds and Amines Prepared by Asymmetric Synthesis Using the SAMP/RAMP Hydrazone Method

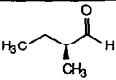
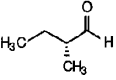
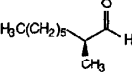
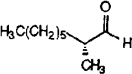
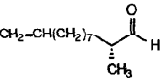
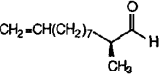

Carbonyl Compound or Amine	Electrophile	Cleavage ^a	Yield ^b [%]	ee[%] (Config.)	Lit.
	$\text{C}_2\text{H}_5\text{I}$	B	71	95 (S)	7a,10a
	CH_3I	A	65	95 (R)	7a,18a
	$\text{C}_6\text{H}_{13}\text{I}$	A	52	≥95 (S)	7a,18a
	CH_3I	A	61	95 (R)	7a,18a
	$(\text{CH}_3)_2\text{SO}_4$	B	65	95 (R)	18a,32
	$(\text{CH}_3)_2\text{SO}_4$	B	51	95(S) ^c	18a,32
	$(\text{CH}_3)_2\text{SO}_4$ CH_3I	A A	66 74	86 (R) 45 (R)	7a 7a

Table I. Continued

Carbonyl Compound or Amine	Electrophile	Cleavage ^a	Yield ^b [%]	ee[%] (Config.)	Lit.
	(CH ₃) ₂ SO ₄ CH ₃ I	A A	70 70	»99 (R) 67 (R)	7a 7a
	CH ₃ I	B	59	94 (R)	7a
	CH ₃ I	C	43	93 (R)	18a,c
	H ₂ O-Cl (CH ₂ I) ₂ Dr	B	20	»89 (R)	19a,20
		B	61	»97 (S)	11
		B	62	»97 (R) ^c	11
		B	46	99 (S)	31

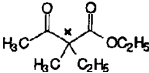
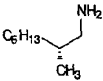
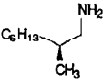
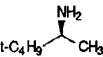
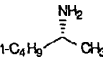
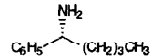
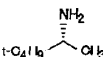
Table I. Continued

Carbonyl Compound or Amine	Electrophile	Cleavage ^a	Yield ^b [%]	ee[%] (Config.)	Lit.
		A	53	>95 (S)	18a,c
		A	80	≥95 (S)	18a,c
	C ₂ H ₅ I	B	44	≥97 (S)	5b
	<i>n</i> -C ₈ H ₁₇ CHO	D	32	62 (-) →100 (-) ^g	20
	C ₅ H ₁₁ CHO	E	75	39 (S) ^c	7b
	C ₆ H ₅ CHO	A	86	72 (SS) [de=67% (SS)]	21
		A	35	de=88-100 (SS) ^f	
	C ₆ H ₅ CHO	A	81	74 (SS) [de=66% (SS)]	21
		A	37	de=88-100 (SS) ^f	

Table I. Continued

Carbonyl Compound or Amine	Electrophile	Cleavage ^a	Yield ^b [%]	ee[%] (Config.)	Lit.
		A	62	≥99 (R)	22
		A	45	≥96 (R)	22
		A	46	≥95 (R)	24
		A	39	>98 (SS) [de ~ 100% (SS)]	23
		A	35 ^g	≥95 (R)	24
		A	30 ^g	≥95 (R)	24
	CH ₃ I	A	65	60 (-)	18a,c

Table I. Continued

Carbonyl Compound or Amino	Electrophile	Cleavage ^a	Yield ^b [%]	ee[%] (Config.)	Lit.
	C ₂ H ₅ I	A	52	27(+)	18a,e
	CH ₃ I	h	56	>90 (R)	26
	C ₆ H ₁₃ Br	h	63	>95 (S)	26
		i	60	90 (S)	18c,d
	-	j	47	88 (R)	18c,d
	-	k	56	85 (R)	27
	-	l	41	87 (R)	27

^aA: Oxidative cleavage by ozonolysis (O_3 , CH_2Cl_2 , $-78^\circ C$). B: Acidic hydrolysis (i. excess MeI , $60^\circ C$, ii. 5 N HCl /pentane). C: Acidic hydrolysis (12 N HCl /ether). D: Oxidative cleavage (1O_2 , Me_2S , hydrolysis). E: Oxidative cleavage (30% H_2O_2 , $MeOH$, pH 7 buffer).

^bOverall chemical yield.

^cRAMP was used as chiral auxiliary.

^dde of corresponding SAMP-hydrazone.

^eAfter two recrystallizations of the ketol.

^fAfter separation and cleavage of the corresponding crystalline SAMP-hydrazone.

^gOverall yield, including reduction of the intermediate β -substituted aldehyde esters and lactonization.

^hThe primary amines are obtained by catechol-borane reduction of the SAMP-hydrazones, followed by N-N bond cleavage with Raney Nickel.

ⁱObtained by $LiAlH_4$ -reduction of 3,3-dimethyl-2-butanone-SAMP-hydrazone, followed by N-N bond cleavage.

^jObtained by catechol-borane reduction of 3,3-dimethyl-2-butanone-SAMP-hydrazone, followed by N-N bond cleavage.

^kObtained by addition of butyllithium to benzaldehyde-SAMP-hydrazone, followed by N-N bond cleavage.

^lObtained by addition of methyllithium to 2,2-dimethylpropanal-SAMP-hydrazone, followed by N-N bond cleavage.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(+)-4-Methyl-3-heptanone: 3-Heptanone, 4-methyl-, (S)- (9); (51532-30-0)

3-Pentanone SAMP-hydrazone: 1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)- (9); (59983-36-7)

SAMP: (S)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine, 2-(methoxymethyl)-, (S)- (9); (59983-39-0)

3-Pentanone (8,9); (96-22-0)

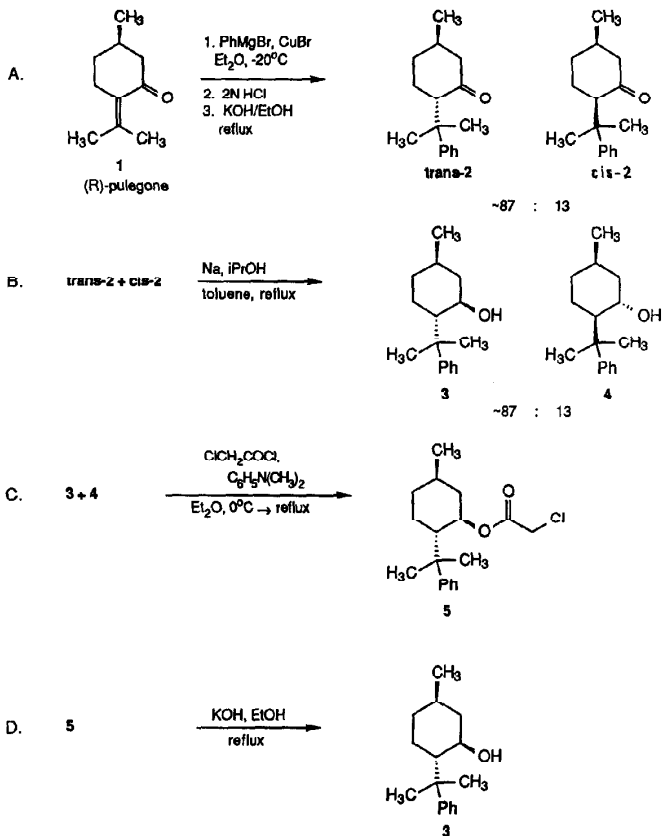
(S)-(+)-4-Methyl-3-heptanone SAMP-hydrazone: 1-Pyrrolidinamine, N-(1-ethyl-2-methylpentylidene)-2-(methoxymethyl)-, [S-[R*,R*-(Z)]]- (10); (69943-24-4)

Propyl iodide: Propane, 1-iodo- (8,9); (107-08-4)

(S)-1-Nitroso-2-methoxymethylpyrrolidine: Pyrrolidine, 2-(methoxymethyl)-1-nitroso-, (S)- (9); (60096-50-6)

(-)-8-PHENYLMENTHOL

(Cyclohexanol, 5-Methyl-2-(1-methyl-1-phenylethyl)-, [1R-(1 α ,2 β ,5 α)]-)



Submitted by Oswald Ort.¹

Checked by Lalith R. Jayasinghe and James D. White.

1. Procedure

Caution! Chloroacetyl chloride is a strong lachrymator. N,N-Dimethylaniline is a severe poison. Synthetic work with these substances should be performed in an efficient hood.

A. (2*RS*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone 2 (Note 1). a) Grignard reagent formation and conjugate addition. In a nitrogen-flushed, 500-mL, two-necked, round-bottomed reaction flask fitted with a reflux condenser carrying a calcium chloride tube, 250-mL pressure-equalizing dropping funnel and Teflon coated magnetic stirring bar are placed 11.0 g (0.45 mol) of magnesium turnings and 50 mL of diethyl ether (Note 2). To this flask is added 1/10 of 78.5 g (0.5 mol) of bromobenzene in one portion (Note 3). The reaction mixture is heated to reflux without stirring to start Grignard reagent formation. When the reaction has started (Note 4), the rest of the bromobenzene in 100 mL of diethyl ether is added with stirring at such a rate that gentle reflux is maintained. After the addition is complete, the reaction mixture is heated to reflux for an additional 1 hr. The solution is cooled to room temperature and diethyl ether is added to give a total volume of about 300 mL (Note 5). The reflux condenser and the dropping funnel are replaced by a nitrogen inlet tube and a pierced rubber septum with Teflon tube inlet (Note 6).

In a second nitrogen-flushed, 500-mL, three-necked, round-bottomed reaction flask with a mechanical stirrer, thermometer, and two-way adapter carrying a calcium chloride tube and a rubber septum with Teflon tube, connected to reaction flask 1 (Figure 1), are placed 4.4 g (31 mmol) of copper(I) bromide (Note 7) and 70 mL of diethyl ether. The ethereal Grignard solution from reaction flask 1 is added, through the Teflon tube by means of

nitrogen pressure (see Figure I). to this vigorously stirred suspension at -20°C . After the addition is complete, the reaction mixture is stirred at -20°C for 1/2 hr. The rubber septum is replaced by a 100-ml, pressure-equalizing dropping funnel containing 40.0 g (0.26 mol) of (R)-(+)-pulegone (Note 8) in 50 mL of diethyl ether. This solution is added with stirring at -20°C to the dark-green reaction mixture during about 2 hr. After the reaction mixture is kept overnight at -20°C , it is added to 300 mL of vigorously stirred ice-cold 2 N hydrochloric acid. The organic layer is separated, filtered with suction and the residue on the funnel is washed twice with 20-ml portions of ether. The aqueous layer is saturated with ammonium chloride and extracted three times with 100-ml portions of ether. The combined organic phases are washed with saturated aqueous sodium hydrogen carbonate solution and the solvent is evaporated under reduced pressure. The crude oily product (~ 62.4 g) is used for equilibration without further purification (Note 9).

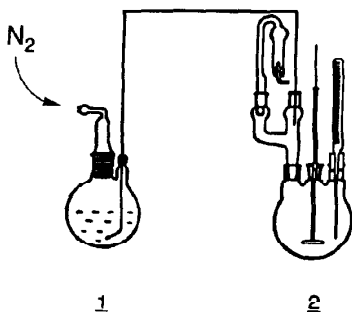


Figure I

b) Equilibration of ketones 2. A solution of 62.4 g of crude 2 in 600 mL of ethanol, 80 mL of water and 70.0 g (1.2 mol) of potassium hydroxide is refluxed for 3 hr. The solution is concentrated on a rotary evaporator to a volume of about 200 mL and 500 mL of water is added. This aqueous solution is saturated with sodium chloride and extracted with four 100-mL portions of ether. The combined organic layers are dried over anhydrous magnesium sulfate and the solvent is evaporated at reduced pressure. The remaining oily liquid is distilled under reduced pressure at 0.05 mm. Three fractions are collected; the first fraction (boiling range 40-80°C) is discarded. Fraction 2 (boiling range: 80-100°C/120°C oil bath temperature) consists mainly of biphenyl with small amounts of ketone 2 (Note 10). Fraction 3 (boiling range: 100-110°C/140°C oil bath temperature) contains the main quantity of ketone 2. Fraction 3 and the decanted liquid of fraction 2 are combined to yield 47.3-54.5 g (79-91%) of pale yellow oily 2 (Note 11).

B. (1*RS*,2*SR*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol 3/4. In a 500-mL, three-necked, round-bottomed reaction flask fitted with a reflux condenser carrying a calcium chloride tube, a 250-mL pressure-equalizing funnel and a mechanical Hershberg stirrer² are placed 16.0 g (0.70 mol) of sodium and 220 mL of toluene (Note 12). The solution is heated to reflux and maintained at this temperature. By vigorous stirring a fine suspension of sodium is obtained. To this stirred suspension a solution of 54.5 g (0.24 mol) of equilibrated 2 in 40.8 g (0.68 mol) of 2-propanol (Note 13) is added dropwise at such a rate that controlled refluxing is maintained. After the addition is complete the reaction mixture is refluxed for an additional 8 hr and then cooled to 0°C. The mixture is diluted with 250 mL of ether (Note 14) and carefully poured into 200 mL of ice-water. The organic layer is separated and the aqueous phase is saturated with sodium chloride and extracted three

times with 100-mL portions of ether. The combined organic layers are washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. Fractional distillation of the concentrate gives 39.0-48.9 g (70-88%) of pale-yellow 3/4, bp 103-107°C/0.01 mm (126°C oil bath temperature) (Note 15).

C. (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate 5 (Note 16). A 250-mL, three-necked, round-bottomed reaction flask fitted with a reflux condenser and calcium chloride tube, 50-mL pressure-equalizing funnel, thermometer and Teflon coated magnetic stirring bar is charged with 20.0 g (86 mmol) of 3/4, 10.5 g (86 mmol) of N,N-dimethylaniline and 30 mL of diethyl ether. This stirred mixture is cooled to 0°C and a solution of 10.5 g (93 mmol) of chloroacetyl chloride in 30 mL of diethyl ether is added at such a rate that this temperature is maintained. After the reaction is stirred at 0°C for an additional 1 hr, the ice-bath is removed and the reaction mixture is allowed to warm to room temperature during which time N,N-dimethylaniline hydrochloride precipitates. The reaction is completed by heating to reflux for 3 hr (Note 17). The solvent is removed under reduced pressure using a rotary evaporator, and the crystalline white residue is dissolved in 60 mL of dichloromethane and 60 mL of water. The phases are separated and the organic phase is washed thoroughly with an equal volume of water; then it is washed until it is acid-free with a saturated aqueous sodium hydrogen carbonate solution. It is concentrated under reduced pressure to give about 25.0 g of a viscous oil, which crystallizes upon addition of 30 mL of 90% aqueous ethanol. The crystals are filtered with suction to yield 18.6-21.8 g (70-82%) of the chloroacetate as a mixture of diastereomers. Diastereo- and enantiomerically pure chloroacetate 5 is obtained in 48% yield by two fractional crystallizations of the diastereomeric chloroacetates from ethanol, mp 82-83°C; $[\alpha]_D^{20} +22.4^\circ$ (CCl₄, c 2.29) (Note 18).

D. (1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol 3. In a 500-mL round-bottomed reaction flask, fitted with a reflux condenser and Teflon coated magnetic stirring bar, 12.8 g (41 mmol) of 5 (48%) is dissolved in a solution of 300 mL of ethanol, 40 mL of water and 4.6 g (82 mmol) of potassium hydroxide. This solution is refluxed for 2 hr. The solution is concentrated at reduced pressure to a volume of ca. 50 mL and 200 mL of water and 100 mL of ether are added. After the ether layer is separated, the aqueous phase is saturated with sodium chloride and extracted with three 50-mL portions of ether. The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and the solvent is evaporated. Kugelrohr distillation of the cloudy residual oil yields 8.9-9.2 g (92-97%) of 3, bp 105-115°C/0.01 mm; $[\alpha]_D^{20}$ -26.4° ± 0.1° (ethanol, c 1.97) (Note 19).

2. Notes

1. Parts A and B of this procedure are based on a communication of E. J. Corey and H. E. Ensley.^{3a}
2. The submitter used diethyl ether distilled from sodium wire.
3. Bromobenzene was purchased from Merck and Company, Inc. and was used without further purification.
4. Sometimes it becomes necessary to add some single crystals of iodine to start the reaction.
5. The concentration of the ethereal Grignard solution was estimated to be 1.38 N, as determined by hydrolysis of an aliquot (1 mL taken by syringe) and titration with 0.1 N hydrochloric acid.
6. The Teflon tube was 3 mm in diameter.

7. Copper(I) bromide was purchased from Fluka AG, Buchs, Switzerland and was not further purified. In previous runs copper(I) iodide was used to give comparable yields.

8. (R)-Pulegone had $[\alpha]_D^{20} +24.6^\circ$ (ethanol, c 1.92) and was obtained from Haarmann & Reimer, Holzminden. The checkers used technical grade (+)-pulegone (82% pulegone content) and obtained 2 in 67-70% isolated yield after equilibration. The submitters thank Haarmann & Reimer, Holzminden, F. R. Germany, for generous gifts of pure and technical grade (+)-pulegone used in their work.

9. An epimeric mixture of diastereomeric ratio 55:45 was determined by ^{13}C NMR spectroscopy.

10. The Grignard-coupling product, biphenyl (mp 70°C , bp $250^\circ\text{C}/760$ mm), crystallizes in the condenser and has to be liquified by warming with a heat gun.

11. The elemental and structural characterization of 2 is as follows: Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{O}$: C, 83.43; H, 9.63. Found: C, 83.61; H, 9.80; IR (liquid film) cm^{-1} : 1712 (C=O); ^1H NMR (CDCl_3) δ : 0.80-2.78 (m, 8 H), 0.90 (d, 3 H, $J = 6$, $\text{CH}_3\text{CH cis-2}$), 0.96 (d, 3 H, $J = 6$, $\text{CH}_3\text{CH trans-2}$), 1.42 (s, 3 H, $\text{CH}_3\text{CPh trans-2}$), 1.43 (s, 3 H, $\text{CH}_3\text{CPh cis-2}$), 1.48 (s, 3 H, $\text{CH}_3\text{CPh cis/trans-2}$), 7.00-7.44 (m, 5 H, aromatic H); ^{13}C NMR (CDCl_3), trans-2 δ : 22.21 (CH_3), 23.52 (CH_3), 26.71 (CH_3), 28.89 (CH_2), 34.51 (CH_2), 36.02 (CH), 38.93 (C_{quat}), 52.13 (CH_2), 59.23 (CH), 125.37, 125.60, 127.87 and 149.71 (aromatic C), 210.31 (C=O); cis-2 δ : 19.03 (CH_3), 23.67 (CH_3), 24.71 (CH_2), 27.23 (CH_3), 31.10 (CH_2), 32.00 (CH), 39.32 (C_{quat}), 50.07 (CH_2), 59.44 (CH), 125.44, 125.72, 128.65 and 149.26 (aromatic C), 211.21 (C=O). An epimeric mixture of diastereomeric ratio 83:17 was determined by ^{13}C NMR spectroscopy. Ketones 2 have n_D^{20} 1.5270-80.

12. Toluene was distilled from sodium.

13. 2-Propanol was refluxed with magnesium methoxide and fractionated.

14. Without this additional solvent the mixture is quite viscous.

15. ^{13}C NMR-spectroscopy indicated a 3/4-ratio of 87:13. Diastereomers

3/4 can be separated by careful medium-pressure silica gel chromatography (petroleum ether/ether; 95:5)^{3b} or by fractional crystallization of the diastereomeric chloroacetates (*vide supra*). For structural characterization see Note 19.

16. This preparation has been modified.^{3c} Compound 5 has also been prepared by using pyridine/4-dimethylaminopyridine in petroleum ether and chloroacetyl chloride in benzene.⁴

17. The submitters suggest that a revised work-up procedure as follows is preferable but it was not checked. At this point 250 mL of ether and 60 mL of water are added to dissolve the salt. The phases are separated and the procedure as described is followed.

18. The structural and elemental characterization of 5 is as follows:
Anal. Calcd for $\text{C}_{18}\text{H}_{25}\text{ClO}_2$: C, 70.00; H, 8.16. Found: C, 69.81; H, 8.20; IR (KBr) cm^{-1} : 1185 (COC) and 1754 (C=O); ^1H NMR (CDCl_3) δ : 0.66-2.24 (m, 8 H), 0.90 (d, 3 H, $J = 6$, CH_3CH), 1.22 (s, 3 H, CH_3CPh), 1.33 (s, 3 H, CH_3CPh), 3.04 and 3.43 (AB, 2 H, $J = 15$, CH_2Cl), 4.91 (dt, 1 H, $J = 10.6, 4$, HCO), 7.00-7.40 (m, 5 H, aromatic CH); ^{13}C NMR (CDCl_3) δ : 21.71 (CH_3), 22.72 (CH_3), 26.18 (CH_2), 29.67 (CH_3), 31.22 (CH), 34.37 (CH_2), 39.36 (C_{quat}), 40.66 (CH_2), 41.43 (CH_2), 50.20 (CH), 75.65 (CH), 124.93, 125.09, 127.79 and 151.43 (aromatic C), 166.17 (C=O).

The submitters report that 2 may be recovered from the mother liquors enriched in the unwanted diastereomer. The mother liquors were saponified to 3/4 as described in section D, followed by dichromate oxidation to 2 in 77-81% yield according to a procedure given for menthone.⁵ However, this recovery was not checked.

19. The optical rotation, $[\alpha]_D^{23} +26.3^\circ$ (ethanol, d 2.02), for the enantiomer of 3 is reported.^{3a} The elemental and structural characterization of 3 is as follows: Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.80; H, 10.27; IR (liquid film) cm^{-1} : 3420 and 3570 (OH); 1H NMR ($CDCl_3$) δ : 0.64-2.06 (m, 9 H), 0.87 (d, 3 H, $J = 6$, CH_3CH), 1.29 (s, 3 H, CH_3CPh), 1.42 (s, 3 H, CH_3CPh), 3.48 (dt, $J = 10, 4$, HCO), 6.97-7.46 (m, 5 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ : 21.95 (CH_3), 25.93 (CH_3), 26.62 (CH_2), 27.33 (CH_3), 31.45 (CH), 34.81 (CH_2), 39.87 (C_{quat}), 45.62 (CH_2), 53.85 (CH), 72.52 (CH), 125.22, 125.52, 127.88 and 150.83 (aromatic C).

3. Discussion

Since its introduction in 1975 by F. J. Corey and H. F. Enslay^{3a} 8-phenylmenthol has found widespread use as a chiral auxiliary in organic syntheses.³ It has proved to be dramatically superior in diastereoface discriminating ability to the commonly used chiral auxiliaries such as menthol, borneol, etc.

However, in spite of its well-documented applicability in asymmetric synthesis, no fully detailed paper has been published so far, concerning the preparation and isolation of enantio- and diastereomerically pure (-)-8-phenylmenthol.

Starting from (R)-pulegone we present herein an efficient three-step synthesis furnishing (-)-phenylmenthol as an easily separable 87:13-mixture of diastereomers in 55-80% overall isolated yield. Separation of the two diastereomers is achieved either by careful medium-pressure chromatography as Corey and Ensley stated,^{3a,b} or, less tediously for greater quantities, by fractional crystallization of the chloroacetic acid esters and successive saponification as described herein.

Since the conversion of (-)-citronellol to (S)-pulegone is reported,⁶ the enantiomeric (+)-8-phenylmenthol likewise may be synthesized. The latter should also be obtainable in a seven-step synthesis starting from (R)-pulegone (48% overall yield) as Corey and co-workers claimed.^{3b}

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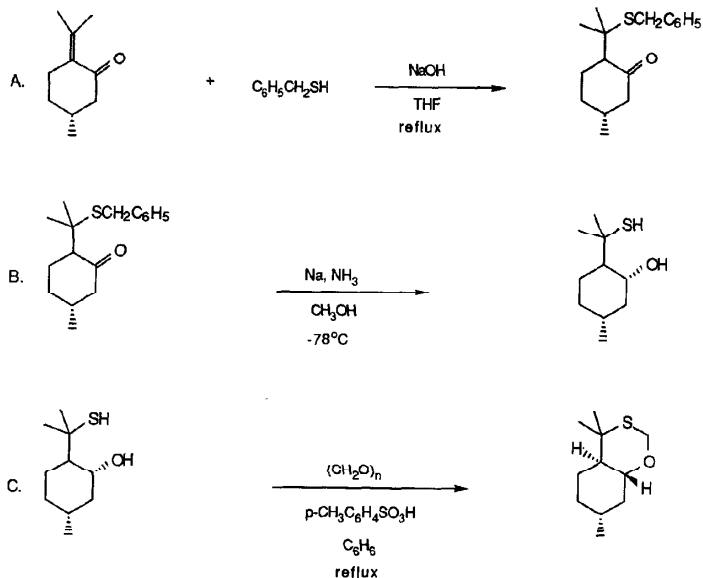
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (-)-8-Phenylmenthol: Cyclohexanol, 5-methyl-2-(1-methyl-1-phenylethyl)-, [1R-(1 α ,2 β ,5 α)]- (10); (65253-04-5)
- (2R,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone: Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)- (10); (57707-92-3)
- (2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanone: Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)- (10); (65337-06-6)
- Magnesium (8,9); (7439-95-4)
- Bromobenzene: Benzene, bromo- (8,9); (108-86-1)
- Copper(I) bromide: Copper bromide (8,9); (7787-70-4)
- (R)-(+)-Pulegone: p-Menth-4(8)-en-3-one, (R)-(+)- (8); Cyclohexanone, 5-methyl-2-(1-methylethylidene)-, (R)- (9); (89-82-7)
- Sodium (8,9); (7440-23-5)
- 2-Propanol (8,9); (67-63-0)
- (1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate: Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester, [1R-(1 α ,2 β ,5 α)]- (10); (71804-27-8)
- N,N-Dimethylaniline: Aniline, N,N-dimethyl-(8); Benzenamine, N,N-dimethyl- (9); (121-69-7)
- Chloroacetyl chloride: Acetyl chloride, chloro- (8,9); (79-04-9)

CHIRAL 1,3-OXATHIANE FROM (+)-PULEGONE: HEXAHYDRO-4,4,7-
TRIMETHYL-4H-1,3-BENZOXATHIIN

(4H-1,3-Benzoxathiin, hexahydro-4,4,7-trimethyl-)



Submitted by Ernest L. Eliel, Joseph E. Lynch, Fumitaka Kume,
and Stephen V. Frye.¹

Checked by Leticia M. Diaz, Stan S. Hall, and Gabriel Saucy.

1. Procedure

Caution! Benzyl mercaptan (Part A) is a foul-smelling liquid. Benzyl mercaptan, the liquid ammonia required in Part B and the benzene employed as a solvent in Part C should be used only in a well-ventilated hood.

A. *cis-* and *trans*-5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]-cyclohexanone (7-benzylthiomenthone). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a Friedrich condenser connected by its upper joint to a mineral oil bubbler through which passes nitrogen gas is charged with 500 mL of tetrahydrofuran (Note 1), 202.0 g (1.33 mol) of (+)-pulegone (Note 2) and 181.0 g (1.46 mol) of benzyl mercaptan (Note 3). The flask is flushed with nitrogen, 10 mL of aqueous 10% sodium hydroxide is added, the flask is stoppered and the mixture is heated to reflux under a static pressure of nitrogen. After 2 hr at reflux the pale yellow solution is allowed to cool, transferred to a 2-L separatory funnel and washed with two 500-mL portions of saturated aqueous sodium chloride. The combined sodium chloride layers, in turn, are extracted with three 250-mL portions of ether, and the combined organic layers are dried over magnesium sulfate for 2 hr, filtered and concentrated by rotary evaporation at aspirator vacuum. The residual liquid is distilled in a good vacuum to give a fraction of bp 167-174°C (0.4 mm) which weighs 325-330 g (89-90%). The product is a mixture of *cis* and *trans* isomers otherwise highly pure as evidenced by spectral analysis (Note 4).

B. 2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol (7-thiomenthol). A 5-L, three-necked, round-bottomed flask is equipped with a variable speed Hershberg stirrer and a 500-mL Dewar condenser filled with dry ice-acetone and connected by its upper joint to a mineral oil bubbler through which passes dry nitrogen gas. The flask is immersed in a dry ice-acetone bath, flushed well with nitrogen and 3000 mL of ammonia is condensed into the flask via a glass tube passed through a rubber septum in the remaining neck of the flask (Note 5). Clean sodium, 125 g (5.43 g-atom), is added slowly to the ammonia with

slow stirring (Note 6). Then 250.3 g (0.906 mol) of *5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone and 72.5 mL (1.8 mol) of methanol in 625 mL of anhydrous ether (Note 7) are added dropwise via a pressure-equalized addition funnel over 5 hr to the vigorously stirred (ca. 500 rpm) solution (Note 8). Stirring is continued an additional 30 min following which 150 mL of methanol is added over 2.5 hr dropwise (to avoid a violent eruption). The solution is allowed to warm slowly (Note 9) and the addition funnel and the condenser are removed to allow the ammonia to evaporate overnight. The reaction flask is immersed in an ice bath and 700 mL of water is added cautiously over an hour to the yellow solid left by evaporation of the ammonia (Note 10). The solution is transferred to a 2-L separatory funnel and extracted with two 200-mL portions of ether, which are discarded. The aqueous layer is poured into a mixture of 500 mL of concentrated hydrochloric acid and 1000 g of ice, transferred to a 4-L separatory funnel and extracted with four 200-mL portions of ether. The combined ether extracts are washed with 200 mL of water, 200 mL of saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated by rotary evaporation at aspirator vacuum. The residual liquid is placed under reduced pressure (0.2 mm) for 1 hr to remove the remaining solvent to give 137-140 g (80-82%) of an orange oil that is a diastereomeric mixture of which the major component constitutes 80%, as indicated by ^{13}C NMR (Note 11).

C. Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin. To a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and charged with 325 mL of benzene (Note 12) is added 140.0 g (0.753 mol) of *5-methyl-2-(1-methyl-1-thioethyl)cyclohexanol, 26.0 g (0.87 mol) of paraformaldehyde (Note 13) and 1 g of p-toluenesulfonic acid monohydrate (Note 14). The flask is fitted with a Dean-Stark trap and a Friedrich condenser and the contents are refluxed for

4 hr by which time the benzene distillate is clear. After the solution is cooled, 5 g of anhydrous potassium carbonate is added and the solution is stirred overnight, filtered, concentrated by rotary evaporation, and the residual liquid is distilled in a good vacuum to give a fraction of bp 69-94°C (0.1 mm), which weighs 130-134 g (86-89%) (Note 15). This fraction is dissolved in 250 mL of pentane, cooled to -25°C and seeded with a crystal of the product (Note 16). Crystallization is allowed to proceed in a freezer with collection and concentration of the mother liquor to half the original volume being carried out every other day to yield, after four crystallizations, 55-60 g (37-40%) of the spectrally pure product (Note 17).

2. Notes

1. Tetrahydrofuran was gold label from Aldrich Chemical Company, Inc.

2. (+)-Pulegone was obtained from SCM Corporation, Jacksonville, FL or Givaudan Corporation, Clifton, NJ; the specific rotation ranged from +21.85 to 22.6°. The material is also available from Aldrich Chemical Company, Inc. Pure pulegone has² $[\alpha]_D^{23} +22.5^\circ$. The discrepancy if any is probably due to chemical impurities since the pulegone used has been shown to be enantiomerically pure.^{3,4} The checkers used (+)-pulegone from Givaudan Corporation, $[\alpha]_D^{20} +25.7^\circ$, which was 94.1% pure (GLC) and contained 4.8% of isopulegone or carvone.

3. Benzyl mercaptan was used as received from Aldrich Chemical Company, Inc.

4. Spectral data; IR (film), cm^{-1} : 1708, 1620, 1500, 1458, 1382, 1363, 1120, 710, and 695; ^{13}C NMR (50 MHz, CDCl_3) δ : 22.2, 23.8, 27.8, 29.6, 33.1, 34.5, 36.6, 48.0, 52.3, 57.8, 126.8, 128.4 (2 C), 128.9 (2 C), 138.7, and 210.2; ^1H NMR (200 MHz, CDCl_3) δ , partial: singlets at 1.38, 1.60, and 3.73, and an intense doublet at 0.97 ($J = 5.9$). The checkers noted that the product distillate was a pale blue color, which turned pale yellow after a few minutes.

5. The submitters noted that at least 15 kg of dry ice was required for a reaction of this scale. Using the described apparatus the checkers found that the distillation of the ammonia required 8-10 hr, which could be reduced to ca. 5 hr by using the following assembly. An oven-dried, 5-L, three-necked, round-bottomed flask was equipped with a glass stirrer shaft fitted with a sleeve joint and a large Teflon blade and the shaft was connected to an overhead motor drive. The flask was also connected to two 450-mL Dewar condensers with a large soda lime drying tube attached to the tube connector of one condenser while the tube connector of the other condenser was attached with Tygon tubing that led through a tower of solid potassium hydroxide pellets to a tank of anhydrous ammonia. While ammonia was slowly flushed through the entire assembly, the Dewar condensers were filled with dry ice-acetone and a dry ice-acetone bath was raised to cool the vessel by immersion. The ammonia flow-rate was increased to condense ca. 3000 mL of ammonia into the flask. Then the condenser with the inlet connection from the ammonia was removed and the flask sealed with a glass stopper.

6. Sodium was stored under mineral oil and washed with pentane before use. For convenience the checkers used 1/6 to 1/4 inch sodium spheres (Matheson Coleman and Bell) that were weighed in mineral oil, then wiped free of oil, rinsed in hexane, cut in half, rinsed in hexane again, and immediately added to the reaction over a 2-hr period; during which time the dark-black mixture became extremely viscous.

7. At this point the checkers charged an oven-dried, 1000-mL pressure-equalizing addition funnel with the ketone in methanol and ether, and then quickly mounted the sealed funnel on the reaction flask by removing the flask's glass stopper.

8. Methanol was used as received from Fisher Scientific, Inc. Anhydrous ether was used as received from freshly opened containers from Mallinckrodt, Inc. and Fisher Scientific, Inc.

9. It is important to let the reaction mixture warm slowly; otherwise the ammonia will boil violently and carry some of the reaction material out of the flask.

10. This reaction is highly exothermic and caution should be exercised since some active sodium may occasionally be left on the sides of the flask.

11. The intense ^{13}C NMR (50 MHz, CDCl_3) signals of the major isomer are at 21.9, 26.9, 29.0, 31.3, 34.5, 34.6, 45.4, 54.6 and 72.9 ppm relative to TMS; ^1H NMR (200 MHz, CDCl_3) δ , partial: 0.91 (d, 3 H, $J = 6.5$), 1.40 (s, 3 H), and 1.52 (s, 3 H).

12. Benzene was used as received from Aldrich Chemical Company, Inc.
Caution! See benzene warning in *Org. Synth.* 1978, 58, 168.

13. Paraformaldehyde was used as received from Aldrich Chemical Company, Inc.

14. p-Toluenesulfonic acid monohydrate was used as received from Aldrich Chemical Company, Inc.

15. Excess paraformaldehyde may separate from the distillate. If this occurs, the liquid should be filtered prior to crystallization.

16. In the absence of seeding, crystallization may take several weeks. It is preferable to separate a small sample of the precursor thiomenthol from its stereoisomers by HPLC (3% ethyl acetate in hexane as eluant) and prepare a small amount of pure oxathiane from this material. Alternatively, a small amount of the product may be purified by GLC on a 5% FFAP column. The melting point of pure material is 37-38°C. The checkers, who did not have seeding crystals, found that the early crops of crystals melted when the flask was allowed to warm to ambient temperature. Consequently the cold supernatant liquid was withdrawn from the crystals with a Pasteur pipette while the flask was maintained at ca. 0°C (ice-water bath). The crystals were subsequently recrystallized several times in the same flask without filtration. By this technique, white crystals melting at 32-35°C were obtained; this material is spectrally pure and suitable for asymmetric synthesis. The supernatant liquid was also concentrated, as the submitters described, to obtain additional crops using this technique.

17. Spectral data; IR (film), cm^{-1} : 2970-2870, 1455, 1440, 1388, 1370, 1355, 1305, 1155, 1095, 1066, 985, 955, 900, 830, and 710; ^{13}C NMR (50 MHz, CDCl_3) δ : 21.8, 22.1, 24.4, 29.4, 31.3, 34.7, 41.8 (2 C), 51.5, 67.1, and 76.7 ppm; ^1H NMR (200 MHz, CDCl_3) δ partial: 0.92 (d, 3 H, $J = 6.5$), 1.27 (s, 3 H), 1.43 (s, 3 H), 3.35 (td, 1 H, $J = 10.5, 4.2$, HCO), 4.69 (d, 1 H, $J = 11.5$, SCH_2O), 5.03 (d, 1 H, $J = 11.5$, SCH_2O).

3. Discussion

Hexahydro-4,4,7-trimethyl-4H-benzoxathiin is used as a chiral template in the asymmetric synthesis, in over 90% enantiomeric excess, of tertiary^{3,5} and secondary⁶ α -hydroxy aldehydes, $RR'C(OH)CHO$ and the derived acids, $RR'C(OH)CO_2H$ and glycols, $RR'C(OH)CH_2OH$.⁷ The present procedure is a slight modification of a published⁵ one.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-Pulegone: p-Menth-4-(8)-en-3-one, (R)-(+)- (8); Cyclohexanone, 5-methyl-2-(1-methylethylidene)-, (R)- (9); (89-82-7)

Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin: 4H-1,3-Benzoxathiin, hexahydro-4,4,7-trimethyl- (9); (59324-06-0)

Benzyl mercaptan: α -Toluenethiol (8); Benzenemethanethiol (9); (100-53-8)

cis- and trans-5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone: Cyclohexanone, 5-methyl-2-[1-methyl-1-[(phenylmethyl)thio]ethyl]-, (2R-trans)-(10); (79563-58-9); (2S-cis)- (10); (79618-04-5)

2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol: Cyclohexanol-2-(1-mercapto-1-methylethyl)-5-methyl-, [1R-(1 α , 2 α , 5 α)]- (10); (79563-68-1); [1R-(1 α , 2 β , 5 α)]- (10); (79563-59-0); [1S-(1 α , 2 α , 5 β)]- (10); (79563-67-0)

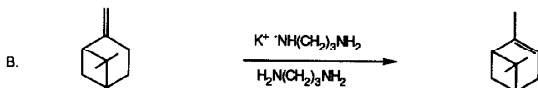
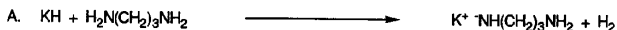
Ammonia (8,9); (7664-41-7)

Sodium (8,9); (7440-23-5)

Paraformaldehyde: Poly(oxymethylene) (8,9); (9002-81-7)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

(-)- α -PINENE BY ISOMERIZATION OF (-)- β -PINENE



Submitted by Charles A. Brown¹ and Prabhakar K. Jadhav.²

Checked by Janet W. Grissom and Edwin Vedejs.

1. Procedure

Caution! Potassium hydride³ is highly reactive toward water. Material separated from protective oil or solvent should not be exposed to air, but should be kept under argon or nitrogen.

A. *Potassium 3-aminopropylamide (KAPA).* To a bottle of 22.4% potassium hydride in oil (Note 1) is added a Teflon-covered magnetic stirring bar. The contents are agitated by first shaking and then stirring until a visually uniform dispersion is attained. Then 17.8 g (0.10 mol) of the dispersion is transferred (Note 2) to an oven-dried 250-mL flask, fitted with a magnetic stirring bar (Notes 3 and 4), a septum-capped inlet, and an adapter connected to a pressure relief bubbler (mercury or oil). The apparatus is purged with dry argon or nitrogen (Note 5). The flask is charged with 100 mL of dry pentane or other volatile hydrocarbon solvent, and the contents are stirred thoroughly. The stirrer is stopped to allow the potassium hydride to settle, assisted by gentle tapping on the flask, and the supernatant liquid is drawn

off with a double-ended needle under inert gas pressure. This procedure is repeated twice to complete removal of the oil. Residual solvent is then removed in a stream of dry gas. To the dry potassium hydride powder is added rapidly 100 mL of dry 3-aminopropylamine (Note 6). *Caution! Hydrogen gas evolution.* Hydrogen evolution commences immediately (Note 7) and subsides after 1.5 to 2 hr. Formation of KAPA is complete at this time.

B. (-)- α -Pinene. Concurrently, a 3-L, three-necked, round-bottomed flask (fitted with a septum-capped adapter, gas-tight mechanical stirrer, and a tube adapter connected to a gas bubbler) is purged with inert gas (Notes 3 and 4). The flask is then charged with 1,588 mL of (-)- β -pinene (Note 8). To the vigorously stirred pinene at 25°C is added the KAPA (0.1 mol) prepared in Part A, using a double-ended needle, over 15 min. The reaction mixture is stirred for 24 hr at 25°C and is then quenched by addition of 100 mL of ice-cold water. The reaction mixture is transferred to a separatory funnel, washed with two 100-mL portions of water, and dried with anhydrous calcium chloride. The crude pinene is decanted from the calcium chloride through a plug of glass wool and distilled at reduced pressure from lithium aluminum hydride (Notes 8 and 9). The yield of (-)- α -pinene, bp 72-73°C (46 mm), $[\alpha]_D^{23}$ -47.45° (neat, 92% ee), is 1,264 g (93%). The chemical and isomeric purity is 99% by GLC (Notes 10 and 11).

2. Notes

1. Potassium hydride in oil is available from Aldrich Chemical Company, Inc. and Alfa Products, Morton/Thiokol Inc. Material from both sources has been used successfully in this preparation.

2. Potassium hydride dispersion is transferred with a 20- or 30-mL syringe fitted with a 16-gauge needle. The plunger should be lubricated with mineral oil. The density of the potassium hydride dispersion is nearly 1.0 g/mL. Alternatively, a glove box or bag may be used for direct weighing.

3. Teflon is attacked superficially by KAPA with darkening of the surface and of the solution in contact with it. The reactivity of the KAPA is not affected. Polyethylene is not affected at all.

4. All equipment should be dried in an oven and cooled in a desiccator or under dry nitrogen.

5. From this point until the quenching of the final reaction operations must be carried out under argon or nitrogen.

6. For this reaction the amine (Aldrich Chemical Company, Inc.) from a freshly opened bottle is dried by distillation from active powdered calcium hydride. Addition over 1 min or less is required to avoid excessive foaming which has been observed when slow or dropwise addition is used. Older samples of amine which contain water should be pre-dried overnight with potassium hydroxide.

7. A cool (10-15°C) bath should be available to moderate the reaction if foaming occurs. Some samples of potassium hydride which have been exposed to air react sluggishly. Here application of a warm (35-40°C) bath is helpful.

8. The (-)- β -pinene used in this procedure was obtained from Glidden Organics. It was purified before use by distillation from lithium aluminum hydride; small increments of hydride were added to pinene stirred under nitrogen until an excess was present as determined by observing gas evolution on addition of a few drops of methanol to an aliquot of the slurry. The purified material had $[\alpha]_D^{23} -21.0^\circ$ (neat, 92.1% ee). GLC analysis (10% SE-30 on Chromosorb W, 100°C) showed only one peak. Use of dry, peroxide-free

pinene is critical to the success of this procedure. The (-)- β -pinene is also available from Aldrich Chemical Company, Inc. In separate experiments, (-)- β -pinene samples from Aldrich Chemical Company, Inc. and Fluka A.G. were used successfully. The checkers used Aldrich β -pinene and obtained product with $[\alpha]_D^{30} - 46.3^\circ$.

9. Distillation from lithium aluminum hydride serves to remove completely all traces of water and amine as is required for preparation of chiral organoboranes.

10. For GLC conditions see Note 8.

11. The reaction has been carried out at 0°C on a 0.33-mol scale using a vigorous magnetic stirrer for 4 hr.⁴ Under these conditions the isomeric purity was >99.5%. Because the reaction takes place in a two-phase system, the reaction rate appears to be stirrer-dependent and vigorous agitation is essential.

3. Discussion

β -Pinene is an important auxiliary for directed chiral syntheses. It has been used for preparation of mono- and diisopinocampheylborane⁵ β -allyldiisopinocampheylborane,⁶ β -pinanyl-9-bora[bicyclo]nonane,⁵ *cis*-pinanediol,⁷ and 2-hydroxypinan-3-one.⁸

Although both enantiomers of α -pinene occur in nature, only the (+)-enantiomer is commercially available with acceptable enantiomeric purity (92-95%). The (-)-enantiomer is only readily available with 80-85% enantiomeric purity, which is impractical for use in asymmetric syntheses via organoboranes.

Fortunately, (-)- β -pinene of high enantiomeric purity (90-95%) is commercially available and can be isomerized to the thermodynamically more stable (-)- α -pinene. The isomerization has been achieved by use of several acidic, basic, and metal catalysts.⁴ These methods have various limitations such as partial racemization, low chemical yields, and vigorous reaction conditions. The current procedure is based on our earlier report using KAPA at 0°C on a much smaller scale.⁴ The change to 25°C from 0°C was made to simplify the reaction conditions by eliminating the need for external cooling. The reaction has also been carried out on somewhat reduced scale (1-5 mol) using a magnetic stirrer in place of the mechanical stirrer.

1. Chemical Dynamics Dept., IBM Research Laboratory K34-281, 5600 Cottle Road, San Jose, CA 95193.
2. Richard B. Wetherill Chemistry Laboratory, Purdue University, West Lafayette, IN 47907.
3. For a general discussion on metallation with and handling of potassium hydride see: Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.
4. For a general discussion on methods of isomerization of β -pinene to α -pinene see: Brown, C. A. *Synthesis* **1978**, 754.
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7. Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

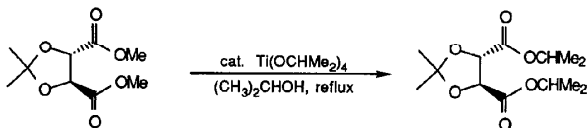
(-)- α -Pinene: 2-Pinene, (1S,5S)-(-) (8); Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (1S)- (9); (7785-26-4)

(-)- β -Pinene: Bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-, (1S)- (9); (18172-67-3)

Potassium hydride (8,9); (7693-26-7)

3-Aminopropylamine: 1,3-Propanediamine (8,9); (109-76-2)

DIISOPROPYL (2S,3S)-2,3-O-ISOPROPYLIDENETARTRATE
(1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl ,
bis(1-methylethyl)ester, (4R-trans)-)



Submitted by René Imwinkelried, Martin Schiess, and Dieter Seebach.¹

Checked by Iseo Kurimoto and Ryoji Noyori.

1. Procedure

A dry, 500-mL, two-necked flask equipped with a magnetic stirrer and a reflux condenser is flushed with nitrogen and charged with 8.4 mL (45.8 mmol) of dimethyl (2S,3S)-2,3-O-isopropylidenetartrate (Note 1) and 250 mL of absolute 2-propanol (Note 2). To the resulting solution is added with a plastic syringe and hypodermic needle 1.35 mL (4.6 mmol) of tetraisopropyl titanate (Note 1). The mixture is refluxed with stirring for 2 hr. To remove the methanol formed, the flask is transferred to a rotary evaporator, and the contents are concentrated to 10 to 12 mL. The oily residue is once more dissolved in 250 mL of absolute 2-propanol (Note 2) and refluxed for 2 hr. The solvent is removed again in a rotary evaporator, and the resulting yellow oil is dissolved in 100 mL of diethyl ether. After addition of 5 mL of water (Note 3) the pale mixture is vigorously stirred for 10 min and then dried over anhydrous magnesium sulfate. The flaky suspension is filtered and the filter-cake washed with three 25-mL portions of ether. The ether solution is

concentrated in a rotary evaporator. The residue, 12.5-13.1 g of a slightly yellow oil, solidifies on standing. This solid is freed from small amounts of solvent by an oil-pump vacuum (ca. 0.01 mm) at room temperature for 2 hr. Further purification by short-path distillation at 91-93°C/0.05 mm furnishes 11.5-12.0 g (91-95%) of a slightly yellow solid, which turns colorless upon crushing, mp 41.5-42.5°C, $[\alpha]_D^{25} +42 \pm 0.3^\circ$ (CHCl_3 , c 4).

2. Notes

1. Commercial (Fluka purum) (-)- or (+)-dimethyl 2,3-O-isopropylidene-tartrate and tetraisopropyl titanate can be used without further purification.

2. 2-Propanol was heated at reflux over CaSO_4 , distilled, and redistilled with addition of tetraisopropyl titanate (ca. 10 g/L).

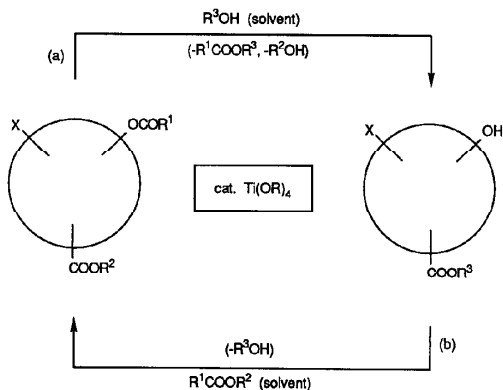
3. This is done to hydrolyze titanium alkoxides. Part of the titanium alkoxides is removed during evaporation of the solvents in the rotatory evaporator $[\text{Ti}(\text{OCHMe}_2)_4$, bp 78°C/12 mm].

3. Discussion

Normally, transesterifications are acid- or base-catalyzed, e.g., sulfuric acid, p-toluenesulfonic acid, and potassium or sodium alkoxides in the appropriate alcohols.² These methods fail with molecules containing acid- or base-labile functional groups. The titanate-mediated esterifications, deacylations, and transesterifications of rather simple, monofunctional substrates are described in the patent literature; see the references in a recent article.³ Recently, Seebach, et al.^{3,4,5} have demonstrated that this method is applicable also to substrates with additional functional groups

which would not survive acid- or base-catalyzed transesterification conditions, such as $C\equiv C$ and $C\equiv N$ bonds, acetals, β -hydroxy and β -acyloxy esters, β -lactams, tert-butyldimethylsilyloxy groups, BOC⁶ and other carbamate protecting groups, etc. In the accompanying Scheme, the possible applications of this transesterification are illustrated, and some characteristic examples are given in the Table. Of course, the method can only establish equilibrium conditions. Therefore, depending on the particular case, components of the equilibria have to be removed (see procedure above) or used in large excess to drive the conversion to the desired products.

Scheme

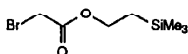


Titanate-mediated Transesterifications

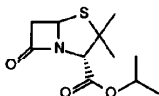
X = Functional group (see accompanying text)

- (a) Transesterification in alcoholic solvents, with removal of acyl protecting groups and exchange of the alcohol component of ester groups in the substrate.
- (b) Transesterification in ester solvents, with acylation of hydroxy groups and exchange of the alcohol or of the acid component of ester groups in the substrate.

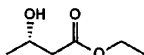
Table I. Products of Transesterification with Titanate Catalysis³⁻⁶



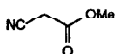
71% from ethyl ester
and 2-trimethylsilylethanol



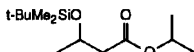
91% from methyl ester
and 2-propanol



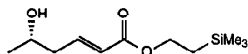
90% from O-3,5-dinitrobenzoate
and ethanol



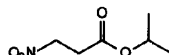
88% from ethyl ester
and methanol



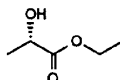
83% from ethyl ester
and 2-propanol



74% from methyl ester
and 2-trimethylsilylethanol



50% from methyl ester
and 2-propanol



60% from O-propanoyl
derivative and ethanol



70% from alcohol
and ethyl acetate



89% from methyl ester
and benzyl alcohol

1. Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.
2. Palai, S., Ed. "The Chemistry of Acid Derivatives", Supplement B, Part 1; Interscience Publishers: New York, 1979.
3. Seebach, D.; Hungerbühler, E., Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. F. *Synthese* **1982**, 138.
4. Schnurrenberger, P.; Züger, M. F.; Seebach, D. *Helv. Chim. Acta* **1982**, 65, 1197. See also: Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, 65, 495.
5. Seebach, D.; Weidmann, B.; Widler, L. In "Modern Synthetic Methods 1983". Scheffold, R., Ed.; Otto Salle: Frankfurt, Sauerländer: Aarau, Wiley: New York, 1983; Vol. 3, p. 217.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diisopropyl (2S,3S)-2,3-O-isopropylidenetartrate: 1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, bis(1-methylethyl) ester, (4R-trans)- (11); (81327-47-1)

Dimethyl (2S,3S)-2,3-O-isopropylidenetartrate: 1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester, (4R-trans)- or (4S-trans)- (9); (37031-29-1) or (37031-30-4)

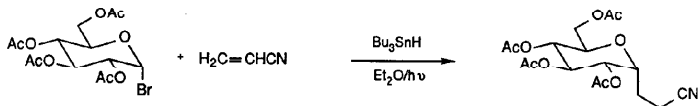
2-Propanol (8,9); (67-63-0)

Tetraisopropyl titanate: Isopropyl alcohol, titanium (4+) salt (8);

2-Propanol, titanium (4+) salt (9); (546-68-9)

1-DEOXY-2,3,4,6-TETRA-O-ACETYL-1-(2-CYANOETHYL)- α -D-GLUCOPYRANOSE

(D-glycero-D-ido-Nonononitrile, 4,8-anhydro-2,3-dideoxy-,
5,6,7,9-tetraacetate)



Submitted by Bernd Giese, J. Dupuis, and Marianne Nix.¹

Checked by John P. Daub and Bruce E. Smart.

1. Procedure

Caution! Acrylonitrile is an OSHA-regulated carcinogen and appropriate precautions should be taken in handling this substance.

A 250 mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, dry nitrogen inlet, reflux condenser, and septum is flushed with nitrogen and charged with 20.6 g (50 mmol) of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (Note 1) and 100 mL anhydrous ether. The mixture is brought to reflux with a heat gun. A nitrogen atmosphere is maintained over the reaction mixture during this and the ensuing steps. When the 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide dissolves, 13.5 g (250 mmol) of acrylonitrile and 16.0 g (55 mmol) of tributyltin hydride (Note 2) are added by means of a syringe. The refluxing solution is irradiated with a sunlamp positioned 2.5–3.8 cm from the reaction flask (Note 3). The heat from the sunlamp maintains a vigorous reflux. After 4 hr, the irradiation is stopped and the reaction mixture is cooled and filtered to collect the precipitated

crystals (Note 4). The filtrate is reintroduced under nitrogen into the reaction vessel. An additional 6.6 g (120 mmol) of acrylonitrile and 5.8 g (20 mmol) of tributyltin hydride are added and irradiation is resumed for another 4 hr until the starting bromide is completely reacted (Note 5). After the reaction mixture is cooled, it is filtered, the filtrate is saved, and the filter cake (Note 6) is combined with the crystals collected above. The solids are stirred with 250 mL of hot isopropyl alcohol and filtered. The hot filtrate is concentrated to a total volume of 75 mL, allowed to cool and filtered to give 7.8-8.6 g (40-45%) of 1-deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- α -D-glucopyranose as long, colorless crystals, mp 121-122°C, $[\alpha]_D^{25} +66.2$ (CHCl₃, c 0.7) (Note 7). The isopropyl alcohol mother liquor is set aside. The above filtrate from the crude reaction mixture is concentrated, taken up in 50 mL of acetonitrile, and extracted three times with 50-mL portions of pentane. The acetonitrile phase is combined with the isopropyl alcohol mother liquor and concentrated. The resulting syrup is flash-chromatographed on silica gel using ethyl acetate/hexane (1:1) eluent to afford an additional 2.2-2.5 g of pure 1-deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- α -D-glucopyranose after separation of byproducts (Notes 8 and 9). The combined yield of pure product is 53-56%.

2. Notes

1. This material was obtained from the Sigma Chemical Company and was recrystallized from ethyl ether/pentane before use. It also can be prepared by the procedure of Redemann, C. E.; Niemann, C. *Org. Synth., Collect. Vol. III* 1955, 11.

2. Acrylonitrile and tributyltin hydride were obtained from the Aldrich Chemical Company, Inc., and used without further purification. The use of a large excess of acrylonitrile reduced the amount of reduction by-product (2,3,4,6-tetraacetyl-1,5-anhydroglucitol). Because tributyltin hydride also reacts with acrylonitrile, a small excess must be used.

3. The checkers used a 275-watt General Electric sunlamp. The submitters indicate that the type of sunlamp is not critical and that a 125-watt Philips E99/2 sunlamp or a 125-watt Philips 57203 high-pressure mercury lamp are suitable. If the heat from the sunlamp does not maintain reflux, the reaction flask should be about one-fourth submerged into a hot oil bath.

4. During the reaction the amount of precipitate gradually increases until the light from the sunlamp is totally blocked and the reaction stops.

5. The reaction can be followed by TLC using 0.25-mm silica gel 60 F-254 plates (E. Merck & Company) and ethyl acetate/hexane (1:1) eluent: 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (R_f = 0.39); 2,3,4,6-tetra-O-acetyl-1,5-anhydroglucitol (R_f = 0.28); 1-deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- β -D-glucopyranose (R_f = 0.20); 1-deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- α -D-glucopyranose (R_f = 0.16).

6. This solid contains a large amount of insoluble polymer in addition to product.

7. The product is analytically pure: Anal. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.80; H, 6.01; N, 3.63; 1H NMR ($CDCl_3$, 360 MHz) : 1.84-1.95 (m, 1 H, CCH_2), 2.05 (s, 6 H, 2 OAc), 2.09 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.05-2.22 (m, 1 H, CCH_2), 2.46 (m, 2 H, CH_2CN), 3.88 (ddd, 1 H, H_5 , $J_{5,6} = 5.80$, $J_{5,6'} = 2.88$, $J_{4,5} = 8.30$), 4.12 (dd, 1 H, H_6 , $J_{6,6'} = 12.24$), 4.23 (m, 1 H, H_1), 4.32 (dd, 1 H, H_6), 4.98 (t, 1 H, H_4 , $J_{3,4} = 8.30$), 5.09 (dd, 1 H, H_2 , $J_{1,2} = 5.23$, $J_{2,3} = 8.30$), 5.23 (t, 1 H, H_3); IR (KBr) cm^{-1} : 2240 (C N), 1745 (C=O).

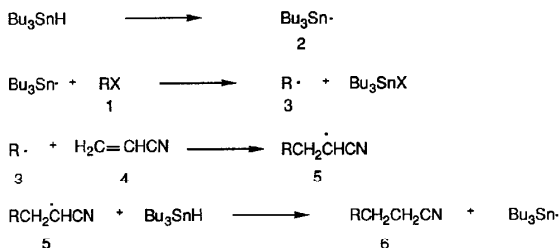
8. E. Merck 230-400 mesh Kieselgel 60 silica gel was used in the flash-chromatography. The first fraction contained 3.5 g (21%) of the tetra-O-acetyl-1,5-anhydroglucitol by-product; the second fraction contained 0.95-1.00 g (5%) of pure 1-deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- β -D-glucopyranose: mp 91-93°C, 117-119°C (two forms); $[\alpha]_D^{25}$ -19.6 (CHCl₃, c 1.01). The final fraction contained the desired product. The ratio of α : β isomers based on isolated yields is 11:1. The submitters report a ratio of 14:1 based on chromatographic analysis of the crude reaction mixture.

9. 1-Deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- β -D-glucopyranose shows IR (KBr) cm^{-1} : 2240 (C \equiv N), 1745 (C=O); ¹H NMR (CDCl₃, 360 MHz) δ : 1.79 (br m, 1 H, CCH₂), 1.92 (br m, 1 H, CCH₂), 2.00 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.52 (m, 2 H, CH₂CN), 3.56 (dt, 1 H, H₁, J_{1,2} = 9.6, J = 9.6, 2.6), 3.68 (ddd, 1 H, H₅, J_{4,5} = 9.9, J_{5,6} = 5.0, J_{5,6'} = 2.1), 4.11 (dd, 1 H, H₆, J_{6,6'} = 12.2), 4.24 (dd, 1 H, H₆), 4.88 (t, 1 H, H₂, J_{2,3} = 9.6), 5.05 (t, 1 H, H₄, J_{3,4} = 9.4), 5.20 (t, 1 H, H₃). Anal. Calcd for C₁₇H₂₃N₃O₉: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.85; H, 6.09; N, 3.70.

3. Discussion

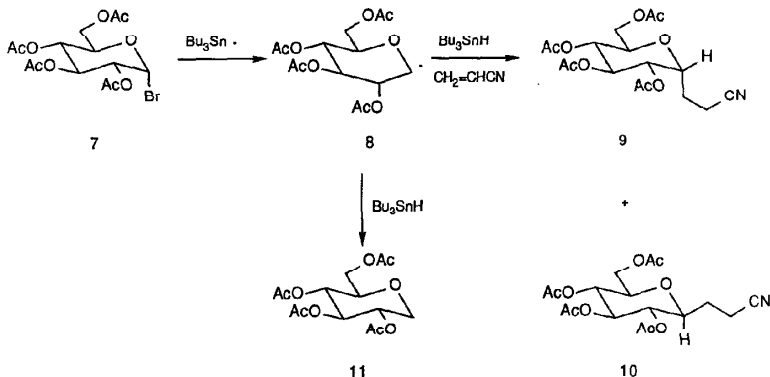
The formation of the C-C bond occurs in a radical chain reaction² (Scheme 1). Bromine abstraction from halide 1 by tin radicals 2³ leads to carbon radicals 3 that react with alkenes 4 to give product radicals 5. Trapping of 5 by tributyltin hydride yields products 6 and the tin radical 2.

Scheme 1



In contrast to anionic 1,4-addition methods, the radical procedure tolerates an acetoxy group adjacent to the reactive center (radical - bearing carbon). In applying this general method to tetraacetylglucosyl bromide 7,⁴ products 9, with an axial C-C bond, and 10 are obtained in a ratio of ca. 10:1. ESR experiments show that the radical intermediate has the boat conformation 8.⁵ The attack that leads to the axial product 9 is, therefore, the favored pseudoequatorial attack,⁶ assuming that the transition state also resembles boatlike 8. Some of the radical 8 is trapped directly by tributyltin hydride to give the simple reduction product 11. This is a common side-reaction in tin hydride-initiated radical coupling reactions.

Scheme 2



This method has been applied also to mannosyl bromide and galactosyl bromide.⁴ Because alkoxyalkyl radicals are nucleophilic radicals, only alkenes with electron-withdrawing substituents can be used.⁷ The 1,5-anhydroglycitol side product 11 is formed in amounts that increase with the decreasing reactivity of alkene 4.

1. Institut für Organische Chemie und Biochemie. TH Darmstadt. Petersenstrasse 22, D-6100 Darmstadt, Germany.
2. Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem.* **1984**, *96*, 51; *Angew. Chem. Intern. Ed. Engl.* **1984**, *23*, 69; Giese, B. *Angew. Chem.* **1985**, *97*, 555; *Angew. Chem., Intern. Ed. Engl.* **1985**, *24*, 553.
3. Kulivila, H. G. *Synthesis* **1970**, 499.

4. Giese, B.; Dupuis, J. *Angew. Chem.* **1983**, *95*, 633; *Angew. Chem., Intern. Ed. Engl.* **1983**, *22*, 622.
5. Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem.* **1984**, *96*, 887; *Angew. Chem., Intern. Ed. Engl.* **1984**, *23*, 896.
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7. Giese, B. *Angew. Chem.* **1983**, *95*, 771; *Angew. Chem., Intern. Ed. Engl.* **1983**, *22*, 753.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Deoxy-2,3,4,6-tetra-O-acetyl-1-(2-cyanoethyl)- α -D-glucopyranose:
 D-glycero-D-ido-Nonononitrile, 4,8-anhydro-2,3-dideoxy-, 5,6,7,9-tetraacetate
 (11); (86563-27-1)

Acrylonitrile (8); 2-Propenenitrile (9); (107-13-1)

2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide: Glucopyranosyl bromide
 tetraacetate. α -D- (8): α -D-glucopyranosyl bromide. 2.3.4.6-tetraacetate (9):
 (572-09-8)

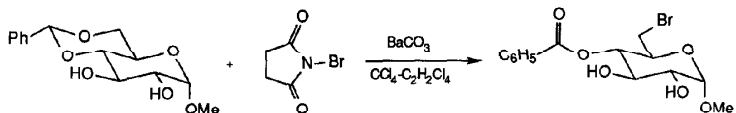
Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

6-BROMO-6-DEOXY HEXOSE DERIVATIVES BY RING-OPENING OF

BENZYLIDENE ACETALS WITH N-BROMOSUCCINIMIDE:

METHYL 4-O-BENZOYL-6-BROMO-6-DEOXY- α -D-GLUCOPYRANOSIDE

(Glucopyranoside, methyl 6-bromo-6-deoxy-, 4-benzoate, α -D-)



Submitted by S. Hanessian.¹

Checked by Janice Cammack and James D. White.

1. Procedure

To a suspension containing 20.5 g (72.61 mmol) of methyl 4,6-O-benzylidene- α -D-glucopyranoside (Note 1) in 1 L of carbon tetrachloride and 60 mL of 1,1,2,2-tetrachloroethane (Note 2) are added 15 g (84.27 mmol) of N-bromosuccinimide and 8 g (31.13 mmol) of barium carbonate. The resulting suspension is heated at the reflux temperature of the mixture with mechanical stirring for a period of 2.5 hr and filtered while hot. During the initial period of heating, a reddish orange color develops but fades before termination of the reaction. The yellowish gummy residue in the flask is washed with two 100-mL portions of hot carbon tetrachloride and the filtrate and washings are evaporated under reduced pressure to give a pale yellow oil that is dissolved in 500 mL of ether. The solution is washed with three 60-mL portions of water, then dried over anhydrous sodium sulfate. Evaporation affords a pale yellow oil which crystallizes (Note 3) upon trituration with

cold ether to yield 12.1 g of white crystals, mp 120-123°C. A second crop of 1.72 g is obtained from the mother liquors (Note 4). Recrystallization of 1 g of product by dissolution in a minimum volume of acetone and addition of ether, then pentane gives 0.9 g of white crystals, mp 131-132°C; $[\alpha]_D^{25} +118^\circ$ (CHCl₃, c 1).

2. Notes

1. The preparation of methyl 4,6-O-benzylidene- α -D-glucopyranoside follows essentially the procedure reported.²

A mixture of 60 g (0.31 mol) of methyl α -D-glucopyranoside, 45 g of freshly fused and powdered zinc chloride, and 150 mL of benzaldehyde ("practical" grade) is stirred at room temperature for a period of 48 hr. The resulting pale yellow, cloudy reaction mixture is poured slowly, with stirring, into 1.25 L of cold water, stirred for an additional 10 min, and refrigerated overnight. Hexane (75 mL) is added and the resulting mixture is stirred for 0.5 hr to aid in removing excess benzaldehyde. The product is separated on a Buchner funnel, washed twice with 100 mL of cold water, and dried under vacuum at room temperature overnight. Recrystallization from chloroform-ether affords 55 g (63% yield) of analytically pure material, mp 164-165°C.

2. Carbon tetrachloride (spectral grade) was passed through a thick layer of Woelm alumina (neutral). 1,1,2,2-Tetrachloroethane was used as a cosolvent to aid in the dissolution of the starting sugar derivative. In other instances carbon tetrachloride was the solvent.

3. Crystallization did not occur if traces of tetrachloroethane were present. The checkers found it necessary to evaporate at ~ 0.05 mm in a warm water bath for ~ 2 hr to remove residual solvent.

4. Evaporation of the mother liquors and flash column chromatography (350 mL of silica gel; column height 28 cm; eluent 70% ethyl acetate-hexanes, fraction size, 30 mL), give additional (1.87 g) product which was eluted with fractions 25-36; total yield 15.69 g, 60%. (Silica gel, Kieselgel 60; E. Merck AG, Darmstadt, Germany.)

3. Discussion

Halogeno sugar derivatives are versatile intermediates for the preparation of aminodeoxy, deoxy, thio and related analogs.³ These transformations are easily achieved in the case of primary halides, which in turn can be prepared by a variety of methods. A number of 6-deoxy and 6-amino-6-deoxy hexoses are components of antibiotics and related natural products.^{4,5} Benzylidene acetals of the 1,3-dioxane or 1,3-dioxolane type undergo a ring opening reaction in the presence of N-bromosuccinimide to give the corresponding O-benzoylated bromohydrins.⁶ This transformation has been known for a number of years in the carbohydrate series (Hanessian-Hullar reaction),⁷ and has been used extensively in synthetic work. In the case of 4,6-O-benzylidene acetals, the products are the 6-bromo-6-deoxy-4-benzoates. Internal acetals of the 1,3-dioxolane type often undergo ring opening to give the two possible regio-isomeric bromo benzoates. The reaction is compatible with a variety of functional and protecting groups (ester, ether, amide, halide, epoxide, etc.). It is also applicable to substrates containing free hydroxyl groups such as the example given above. A unique feature, which arises as a consequence of the nature of the ring opening, is seen in the case of methyl 4,6-O-benzylidene- α -D-galactopyranoside and its derivatives. In this series the benzoate group is found at the C-4 position which has an axial

orientation. Hence one achieves halogenation at the primary position as well as an indirect benzoylation of an axial hydroxyl group in the parent sugar. Other applications have been found in amino sugars and nucleosides. Table I illustrates a selection of such ring-opening reactions. The reaction has also been applied with disaccharide acetals.^{6,8}

Acknowledgments

The author thanks Mrs. Ani Glamyan for valuable technical assistance.

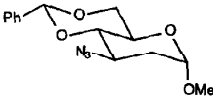
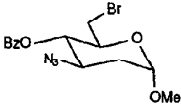
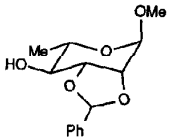
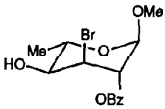
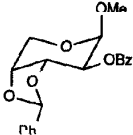
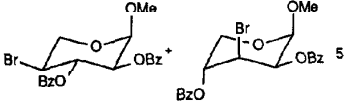
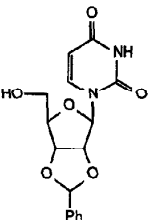
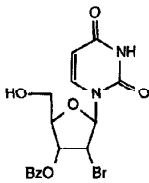
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Table I. Reaction of O-Benzylidene Acetals with N-Bromosuccinimide

Starting Acetal	Product(s)	Reference
		5
		5
		5
		5
		5
		5
		5
		5
		9

Table I (continued). Reaction of O-Benzylidene Acetals with N-Bromosuccinimide

Starting Acetal	Product(s)	Reference
		10
		11
		5
		12

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Methyl 4-O-benzoyl-6-bromo-6-deoxy- α -D-glucopyranoside: Glucopyranoside, methyl 6-bromo-6-deoxy-4-benzoate, α -D- (8); glucopyranoside, methyl 6-bromo-6-deoxy, 4-benzoate, α -D- (9); (10368-81-7)

Methyl 4,6-O-benzylidene- α -D-glucopyranoside: Glucopyranoside, methyl 4,6-O-benzylidene- α -D- (8); α -D-glucopyranoside, methyl 4,6-O-(phenylmethylene)- (9); (3162-96-7)

1,1,2,2-Tetrachloroethane: Ethane, 1,1,2,2-tetrachloro- (8,9); (79-34-5)

N-Bromosuccinimide: Succinimide, N-bromo- (8); 2,5-Pyrrolidinedione, 1-bromo- (9); (128-08-5)

Methyl α -D-glucopyranoside: Glucopyranoside, methyl, α -D- (8);

α -D-glucopyranoside, methyl (9); (97-30-3)

Unchecked Procedures

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- 2350R From Furfural to 3-Substituted 2-Furanones
J.-A. H. Näsman, Institutionen för Organisk kemi
Åbo Akademi, Akademigatan 1, SF-20500 Åbo 50, Finland
- 2358R* Cyclopentanones from Carboxylic Acids via Intramolecular Acylation of Alkylsilanes: 2-Methyl-2-vinylcyclopentanone
I. Kuwajima and H. Iwabe, Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan
- 2363R* Ethyl (E,Z)-2,4-Decadienoate
S. Tsuboi, T. Masuda, and A. Takeda, Department of Synthetic Chemistry, Okayama University, School of Engineering, Okayama, Japan
- 2386* Geranyl Pyrophosphate
A. B. Woodside, Z. Huang, and C. D. Poulter, Department of Chemistry, University of Utah, Salt Lake City, UT 84112
- 2388* (S)-N,N-Dimethyl-N'(1-t-butoxy-3-methyl-2-butyl) Formamidine
D. A. Dickman, M. Boes and A. I. Meyers, Department of Chemistry, Colorado State University, Fort Collins, CO 80523
- 2389 (-)-Salsolidine
A. I. Meyers and M. Boes, Department of Chemistry, Colorado State University, Fort Collins, CO 80523
- 2391 Diastereoselective Formation of α -Methoxycarbonyl Lactones Through an Intramolecular Diels-Alder-Reaction
L. F. Tietze, G. v. Kiedrowski, and K.-G. Fahlbusch, Institut für Organische Chemie, der Georg August Universität, Tammannstrasse 2, D-3400 Göttingen, Federal Republic of Germany
- 2393* 6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one
R. K. Boeckman, Jr., R. B. Perni, J. E. Macdonald, and A. J. Thomas, Department of Chemistry, The University of Rochester, River Station, Rochester, NY 14627
- 2394R* Dienophile Activation via Selenosulfonation. 1-(Benzenesulfonyl)-cyclopentene
H.-S. Lin, M. J. Coglian, and L. A. Paquette, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2395 Prenyltrimethylsilane
C. Biran, J. Gervai, and J. Dunogues, Laboratoire de Chimie Organique du Silicium et de l'Étain, CNRS U.A. 35, Université de Bordeaux I, 351 Cours de la Libération, F-33405 Talence, France
- 2396* Reduction of Carboxylic Acids to Aldehydes: 6-Oxodecanal
T. Fujisawa and T. Sato, Chemistry Department of Resources, Mie University, Tsu Mie 514, Japan
- 2398R* Ethyl α -(Bromomethyl)Acrylate
J. Villieras and M. Rambaud, Synthèse Organique Selective Unité associée au C.N.R.S. n° 475, Faculté de Sciences, F-44072 NANTES Cedex, France

- 2400* Ketones from Carboxylic Acids and Grignard Reagents: Methyl 6-Oxodecanoate
T. Fujisawa and T. Sato, Chemistry Department of Resources, Mie University, Tsu Mie 514, Japan
- 2401 Palladium-Catalyzed Reduction of Enol Trifluoromethanesulfonates to Alkenes: Cholesta-3,5-diene
S. Cacchi, E. Morera, and G. Ortari, Institute of Organic Chemistry, University of Rome, via del Castro Laurenziano 9, 00161 Rome, Italy
- 2402 Cyclopropanation Using an Iron-Containing Methylene Transfer Reagent: 1,1-Diphenylcyclopropane
E. J. O'Connor and P. Helquist, Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556
- 2403* (1-Oxo-2-propenyl)trimethylsilane
R. L. Danheiser, D. M. Fink, K. Okano, Y.-M. Tsai, and S. W. Szczepanski, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139
- 2405* Palladium-Catalyzed Coupling of Acid Chlorides with Organotin Reagents: (E)-Ethyl-4-(4-nitrophenyl)-4-oxo-2-butenolate
A. F. Renaldo, J. W. Labadie, and J. K. Stille, Department of Chemistry, Colorado State University, Ft. Collins, CO 80523
- 2408R* 3-Hydroxy-1-cyclohexenecarboxaldehyde
T. Hudlicky, M. Neveu, D. Pauley, B. C. Ranu, and H. L. Rigby, Department of Chemistry, Virginia Tech, Blacksburg, VA 24061-0699
- 2409* N-Acetyl-N-Phenylhydroxylamine via Catalytic Transfer Hydrogenation of Nitrobenzene using Hydrazine and Rhodium on Carbon
P. W. Oxley, B. M. Adger, M. J. Sasse, and M. A. Forth, Smith Kline and French Research Ltd., Old Powder Mills, Leigh, Tonbridge, Kent, TN11 9AN, England
- 2410* N-Benzyl-N-Methoxymethyl-N-(trimethylsilyl)methylamine as an Azomethine Ylide Equivalent
A. Padwa and W. Dent, Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, GA 30322
- 2413* 4-Chlorination of Electron Rich Benzenoid Compounds
J. R. L. Smith, L. C. McKeer, and J. M. Taylor, Department of Chemistry, University of York, York YO1 5DD, England
- 2414* Alkylations Using (Propargylum)Dicobalt Hexacarbonyl Salts: Preparation of 2-(1-Methyl-2-propynyl)cyclohexanone
V. Varghese, M. Saha, and K. M. Nicholas, Department of Chemistry, The University of Oklahoma, Norman, OK 73019
- 2415* 1,4-Functionalization of 1,3-Dienes: 1-Acetoxy-4-diethylamino-2-butene and 1-acetoxy-4-benzylamino-2-butene
J. E. Nyström, T. Rein, and J.-E. Backvall, Department of Organic Chemistry, Royal Institute of Technology, S-10044 Stockholm, Sweden

- 2416 Titanium Mediated Cyclization of a Diyne: 1,2-E,E-bis(Ethylidene)cyclohexane
W. A. Nugent, Central Research & Development Department, E. I. du Pont de Nemours & Co., Experimental Station, Wilmington, DE 19898
- 2419R* N-tert-Butoxycarbonyl-L-leucinal
O. P. Goel, U. Krolls, M. Stier, and S. Kesten, Warner-Lambert Company, Pharmaceutical Research Division, 2800 Plymouth Road, Ann Arbor, MI 48105
- 2420 Stereoselective 1,4-Functionalizations of Conjugated Dienes: *cis*- and *trans*-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene
J.-E. Backvall and J. Vagberg, Department of Organic Chemistry, Royal Institute of Technology, S-10044 Stockholm, Sweden
- 2421 Palladium-Catalyzed Conjugate Reduction of α,β -Unsaturated Carbonyl Compounds with Diphenylsilane and Zinc Chloride Cocatalyst: α,β -Dihydro- β -Ionone
E. Keinan and N. Greenspoon, Department of Organic Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel
- 2422* Reductive Annulation of Vinyl Sulfones. Bicyclo[4.3.0]non-1-en-4-one
H.-S. Lin and L. A. Paquette, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2424 4-(Trimethylsilyl)-3-buten-1-ol Tetrahydropyranyl Ether, and (Z)-4-(Trimethylsilyl)-3-buten-1-ol
L. E. Overman, T. C. Malone, and S. F. McCann, Department of Chemistry, University of California, Irvine, CA 92717
- 2425 Regioselective Synthesis of Tetrahydropyridines. Synthesis of 1-(4-Methoxyphenyl)-1,2,5,6-tetrahydropyridine
L. E. Overman, C. J. Flann, and T. C. Malone, Department of Chemistry, University of California, Irvine, CA 92717
- 2427* Ethyl 5-Oxo-6-methyl-6-heptenoate from Methacryloyl Chloride and Ethyl 4-Iodobutyrate
Y. Tamaru, H. Ochiai, T. Nakamura, and Z.-i. Yoshida, Department of Synthetic Chemistry, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan
- 2428 α -Diphenylmethylsilylation of Ester Enolates: 2-Methyl-2-undecene from Ethyl Decanoate
G. L. Larson, I. Montes de Lopez-Cepero and L. R. Mies, Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931
- 2429* Ethyl α -(Hexahydroazepinylidene-2) Acetate from O-Methyl-caprolactim and Meldrum's Acid
J. P. Celerier, E. Deloisy-Marchalant, G. Lhommet and P. Maitte, Laboratoire de Chimie des Hétérocycles, Université Pierre et Marie Curie, 4, Place Jussieu, 75230 Paris Cedex 05, France

- 2430* 4,4-Dimethylcyclopent-2-enone
D. Pauley, F. Anderson and T. Hudlicky, Department of Chemistry,
Virginia Tech, Blacksburg, VA 24061-0699
- 2431* 3'-Nitro-1-phenylethanol by Addition of Methyl-triisopropoxy-titanium
to m-Nitrobenzaldehyde
R. Imwinkelried and D. Seebach, Laboratorium für Organische Chemie,
Eidgenössische Technische Hochschule, Universitätsstr. 16,
CH - 8092 Zürich, Switzerland
- 2433* Condensation of (-)-Dimethyl Succinate Dianion with 1,w-Dihalides:
(-)-Dimethyl Cyclopropane-(1S,2S)-1,2-dicarboxylate
K. Furuta, K. Iwanaga, and H. Yamamoto, Department of Applied
Chemistry, Nagoya University, Furocho, Chikusa, Nagoya 464, Japan
- 2434* Synthesis of Cyclobutanones via 1-Bromo-1-ethoxycyclopropane: (E)-2-
(1-Propenyl)cyclobutanone
S. A. Miller and R. C. Gadwood, Department of Chemistry, Northwestern
University, Evanston, IL 60201
- 2438 α -Hydroxylation of Carboxylate Derivatives by Oxygenation of Lithium
Enolates. Ethyl 1-Hydroxycyclohexanecarboxylate
H. H. Wasserman, D. H. Lipshutz, and M. C. Corey, Department of
Chemistry, University of California, Santa Barbara, CA 93106
- 2440 Selective Cyclopropanation of Perillyl Alcohol: 1-Hydroxymethyl-4-
(1-methylcyclopropyl)-1-cyclohexene
K. Maruoka, S. Sakane, and H. Yamamoto, Department of Applied
Chemistry, Nagoya University, Furocho, Chikusa, Nagoya 464, Japan
- 2441 Direct Nucleophilic Acylation by the Low Temperature, in situ
Generation of Acyllithium Reagents; α -Hydroxyketones from Ketones:
Synthesis of 3-Hydroxy-2,2,3-trimethyloctan-4-one from Pinacolone
R. Hui and D. Seyferth, Department of Chemistry, Massachusetts
Institute of Technology, Cambridge, MA 02139
- 2444 Ethynyl p-Tolyl Sulfone
L. Waykole and L. A. Paquette, Department of Chemistry, The Ohio
State University, Columbus, OH 43210
- 2445 Erythro-directed Reduction of β -Keto Amide: Erythro-1-(3-hydroxy-2-
methyl-3-phenylpropanoyl)piperidine
M. Fujita and T. Hiyama, Sagami Chemical Research Center, Nishi-
Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan
- 2446 Threo-directed Reduction of β -Keto Amide: Threo-1-(hydroxy-2-methyl-
3-phenylpropanoyl)piperidine
M. Fujita and T. Hiyama, Sagami Chemical Research Center, Nishi-
Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

CUMULATIVE AUTHOR INDEX

FOR VOLUME 65

This index comprises the names of contributors to Volume 65 only. For authors to previous volumes, see cumulative indices in Volume 64, which covers Volumes 60 through 64, and Volume 59, which covers Volumes 55 through 59, and either indices in Collective Volumes I through V or single volumes entitled *Organic Syntheses, Collective Volumes, I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

- | | |
|---------------------------|-----------------------------|
| Aslamb, M., 65, 90 | Holmes, A. B., 65, 52, 61 |
| Bercaw, J. E., 65, 42 | Hsiao, C.-N., 65, 135 |
| Bergman, J., 65, 146 | |
| Bergman, R. G., 65, 42 | Imwinkelried, R., 65, 230 |
| Block, E., 65, 90 | Jadhav, P. K., 65, 224 |
| Boger, D. L., 65, 32, 98 | Jones, G. E., 65, 52 |
| Bou, A., 65, 68 | |
| Braxmeier, H., 65, 159 | Kellogg, R. M., 65, 150 |
| Brotherton, C. E., 65, 32 | Kendrick, D. A., 65, 52 |
| Brown, C. A., 65, 224 | Kipphardt, H., 65, 173, 183 |
| Buter, J., 65, 150 | Kresze, G., 65, 159 |
| | Kuhlmann, H., 65, 26 |
| Corey, E. J., 65, 166 | Kume, F., 65, 215 |
| | Kuwajima, I., 65, 17 |
| Davidson, S. K., 65, 119 | |
| Dupuis, J., 65, 236 | Le Gal, J. Y., 65, 47 |
| | Lombardo, L., 65, 81 |
| Elie, E. L., 65, 215 | Lynch, J. E., 65, 215 |
| Enders, D., 65, 173, 183 | |
| | Martin, S. F., 65, 119 |
| Fey, P., 65, 173, 183 | McGuire, M. A., 65, 140 |
| Fowler, K. W., 65, 108 | Mickel, S. J., 65, 135 |
| Frye, S. V., 65, 215 | Miller, M. J., 65, 135 |
| | Mukaiyama, T., 65, 6 |
| Georg, G. I., 65, 32 | Mulligan, M. D., 65, 98 |
| Giese, B., 65, 236 | Munsterer, H., 65, 159 |
| Goodwin, G. B. T., 65, 1 | |
| Gross, A. W., 65, 166 | Nakamura, E., 65, 17 |
| | Narasaka, K., 65, 6, 12 |
| Haese, W., 65, 26 | Nix, M., 65, 236 |
| Hanessian, S., 65, 243 | |
| Hegedus, L. S., 65, 140 | |

Olomucki, M., 65, 47
Ort. O., 65, 203

Pericas, M. A., 65, 68
Phillips, G. W., 65, 119

Riera, A., 65, 68
Rodgers, W. B., 65, 108

Sand, P., 65, 146
Schiess, M., 65, 230
Schultze, L. M., 65, 140
Seebach, D., 65, 230
Seidler, P. F., 65, 42
Serratos, F., 65, 68
Smith, G. C., 65, 1
Sporikou, C. N., 65, 61
Stetter, H., 65, 26
Stryker, J. M., 65, 42

Threlkel, R. S., 65, 42

Walshe, N. D. A., 65, 1
Wester, R. T., 65, 108
Woodward, F. E., 65, 1

Ziegler, F. E., 65, 108

CUMULATIVE SUBJECT INDEX

FOR VOLUME 65

This index comprises subject matter for Volume 65 only. For subjects in previous volumes, see the cumulative indices in Volume 64, which covers Volumes 60 through 64, and Volume 59, which covers Volumes 55 through 59, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in brackets. While the systematic name is indexed separately, it also accompanies the common name. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester, [1R-(1 α ,2 β ,5 α)]-, **65**, 203

Acetic acid ethenyl ester, **65**, 135

Acetic acid, trifluoro-, anhydride, **65**, 12

Acetic acid vinyl ester, **65**, 135

ACETONE TRIMETHYLSILYL ENOL ETHER: SILANE, (ISOPROPENYLOXY)TRIMETHYL-; SILANE, TRIMETHYL[(1-METHYLETHENYL)OXY]-; (1833-53-0), **65**, 1

Acetophenone; Ethanone, 1-phenyl-; (98-86-2), **65**, 6, 119

Acetophenone silyl enol ether: Silane, trimethyl[(1-phenylvinyl)oxy]-; Silane, trimethyl[(1-phenylethenyl)oxy]-; (13735-81-4), **65**, 12

4-ACETOXYAZETIDIN-2-ONE: 2-AZETIDINONE, 4-HYDROXY-ACETATE (ESTER): 2-AZETIDINONE, 4-(ACETYLOXY)-; (28562-53-0), **65**, 135

Acetylene; Ethyne; (74-86-2), **65**, 61

Acrylonitrile; 2-Propenenitrile; (107-13-1), **65**, 236

Aldol reaction, **65**, 6, 12

ALLYLCARBAMATES, **65**, 159

1-AMINO-2-METHOXYMETHYLPYRROLIDINE, (R)-(+) - (RAMP), **65**, 173

1-AMINO-2-METHOXYMETHYLPYRROLIDINE, (S)-(-) - (SAMP), **65**, 173, 183

3-Aminopropylamine: 1,3-Propanediamine; (109-76-2), **65**, 224

Asymmetric synthesis, **65**, 183, 215

AZA-ENE REACTION, **65**, 159

2-AZETIDINONE, 4-(ACETYLOXY)-, **65**, 135

2-AZETIDINONE, 4-HYDROXY-ACETATE (ESTER), **65**, 135

2-AZETIDINONE, 3-METHOXY-1,3-DIMETHYL-4-PHENYL-, **65**, 140

Benzaldehyde; (100-52-7), **65**, 119

Benzaldehyde, 2-bromo-4,5-dimethoxy-, **65**, 108

Benzeneamine, 2-methyl-3-nitro-, 65, 146
 Benzenemethanethiol, 65, 215
 2H-1-BENZOPYRAN-3-CARBOXYLIC ACID, 5,6,7,8-TETRAHYDRO-2-OXO-,
 METHYL ESTER, 65, 98
 4H-1,3-BENZOXATHIIN, HEXAHYDRO-4,4,7-TRIMETHYL-, 65, 215
 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride; (4568-71-2),
 65, 26
 Benzylidenemalononitrile: Malononitrile, benzylidene-; Propanedinitrile,
 (phenylmethylene)-; (2700-22-3), 65, 32
 Benzyl mercaptan: α -Toluenethiol; Benzenemethanethiol; (100-53-8), 65, 215
 BETA-LACTAM, 65, 135, 140
 BICYCLO[3.1.1]HEPTANE, 6,6-DIMETHYL-2-METHYLENE-, (1S)-, 65, 224
 BICYCLO[3.1.1]HEPT-2-ENE, 2,6,6-TRIMETHYL-, (1S)-, 65, 224
 [1,1'-BIPHENYL]-2,2'-DICARBOXALDEHYDE, 4,4',5,5'-TETRAMETHOXY-, 65, 108
 1,4-DIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE: 2,7-DISILA OCTA-3,5-DIYNE,
 2,2,7,7-TETRAMETHYL-; SILANE, 1,3-BUTADIYNE-1,4-DIYLBIS[TRIMETHYL-;
 (4526-07-2), 65, 52
 1,2-Bis(trimethylsilyloxy)cyclobut-1-ene: Silane, (1-cyclobuten-1,2-
 ylenedioxy)bis[trimethyl-; Silane, [1-cyclobutene-1,2-
 diylbis(oxy)]bis[trimethyl-; (17082-61-0), 65, 17
 Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF_3)
 (1:1); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1);
 (109-63-7), 65, 17
 2-Bromo 2-butene (cis and trans mixture): 2-Butene, 2-bromo-;
 (13294-71-8), 65, 42

1-Bromo-3-chloro-2,2-dimethoxypropane: 2-Propanone, 1-bromo-3-chloro-, dimethyl acetal; Propane, 1-bromo-3-chloro-2,2-dimethoxy-; (22089-54-9), 65, 2

6-Bromo-3,4-dimethoxybenzaldehyde: Benzaldehyde, 2-bromo-4,5-dimethoxy-; (5392-10-9), 65, 108

6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine, N-[(2-bromo-4,5-dimethoxyphenyl)methylene]-; (73252-55-8), 65, 108

BROMOMETHANESULFONYL BROMIDE: METHANESULFONYL BROMIDE, BROMO-; (54730-18-6), 65, 90

2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane: 1,3-Dioxane, 2-(bromomethyl)-2-(chloromethyl)-; (60935-30-0), 65, 32

N-Bromomethylphthalimide: Phthalimide, N-(bromomethyl)-; 1H-Isoindole-1,3-(2H)-dione, 2-(bromomethyl)-; (5332-26-3), 65, 119

N-BROMOSUCCINIMIDE: SUCCINIMIDE, N-BROMO-; 2,5,-PYRROLIDINEDIONE, 1-BROMO-; (128-08-5), 65, 243

Butadiyne, 65, 52

Butane, 1-chloro-, 65, 61

1-Butanone, 3-hydroxy-3-methyl-1-phenyl-, 65, 6, 12

2-Butene, 2-bromo-, 65, 42

2-Butene, 2-methyl-, 65, 159

2-Buten-1-one, 3-methyl-1-phenyl-, 65, 12

3-Buten-2-one; (78-94-4), 65, 26

tert-Butylhydrazine hydrochloride: Hydrazine, tert-butyl, monohydrochloride; Hydrazine, (1,1-dimethylethyl)-, monohydrochloride; (7400-27-3), 65, 166

N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine: 2-Pentanamine, N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-2,4,4-trimethyl-; (90545-93-0), 65, 166

TERT-BUTYL-TERT-OCTYLAMINE: 2-PENTANAMINE, N-(1,1-DIMETHYLETHYL)-2,4,4-TRIMETHYL-; (90545-94-1), 65, 166

Butyllithium: Lithium, butyl-; (109-72-8), 65, 98, 108, 119

2-BUTYNOIC ACID, 4-CHLORO-, METHYL ESTER, 65, 47

Carbamic acid, dichloro-, methyl ester, 65, 159

CARBAMIC ACID, (2-METHYL-2-BUTENYL)-, METHYL ESTER, 65, 159

Carbamic acid, methyl ester, 65, 159

Carbonic acid, dicesium salt, 65, 150

Carbonochloridic acid, methyl ester, 65, 47

Cesium carbonate: Carbonic acid, dicesium salt; (534-17-8), 65, 150

CESIUM THIOLATES, 65, 150

Chiral auxiliary, 65, 173, 183, 203, 215

1-Chlorobutane: Butane, 1-chloro-; (109-69-3), 65, 61

2-Chloroethanol; Ethanol, 2-chloro-; (107-07-3), 65, 150

2-Chloroethyl dichlorophosphate: Phosphorodichloridic acid, 2-chloroethyl ester; (1455-05-6), 65, 68

Chlorosulfonyl isocyanate: Sulfuryl chloride isocyanate; (1189-71-5), 65, 135

Chlorotetrolic esters, 65, 47

Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4), 65, 1, 6, 61

Chromium carbonyl, 65, 140

Chromium hexacarbonyl: Chromium carbonyl (OC-6-11); (13007-92-6), 65, 140

Chromium, pentacarbonyl(1-methoxyethylidene)-, 65, 140

Copper(I) bromide (7787-70-4), 65, 203

Copper(I) chloride - tetramethylethylenediamine complex, 65, 52

[2 + 2] CYCLOADDITION, 65, 135

Cyclohexanamine, 65, 108

Cyclohexanamine, N-[(2-bromo-4,5-dimethoxyphenyl)methylene]-, 65, 108
 Cyclohexanamine, N-[(2-iodo-4,5-dimethoxyphenyl)methylene]-, 65, 108
 Cyclohexane, 1,1-diethoxy-, 65, 17
 CYCLOHEXANE, 1,2-DIMETHYLENE, 65, 90
 CYCLOHEXANE, 1,2-BIS(METHYLENE)-, 65, 90
 CYCLOHEXANE, 5-METHYL-1-METHYLENE-2-(1'-METHYLETHYL)-, R,R-, 65, 81
 CYCLOHEXANEBUTANOIC ACID, γ -OXO-, ETHYL ESTER, 65, 17
 Cyclohexanol, 2-(1-mercapto-1-methylethyl)-5-methyl-, [(1R-(1 α ,2 α ,5 α)]-,
 65, 215
 Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2 β ,5 β)]-, 65, 81
 CYCLOHEXANOL, 5-METHYL-2-(1-METHYL-1-PHENYLETHYL)-, [1R-(1 α ,2 β ,5 α)]-, 65, 203
 Cyclohexanone; (108-94-1), 65, 98
 Cyclohexanone diethyl ketal; Cyclohexane, 1,1-diethoxy-; (1670-47-9), 65, 17
 Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)-, 65, 81
 CYCLOHEXANONE, 5-METHYL-2-(1-METHYLETHYLIDENE)-, (R)-, 65, 203, 215
 Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)-, 65, 203
 Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)-, 65, 203
 Cyclohexanone, 5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]-,
 (2R-trans)-; (79563-58-9); (2S-cis)-; (79618-04-5), 65, 215
 Cyclohexene, 1-methyl-, 65, 90
 Cyclohexylamine; Cyclohexanamine; (108-91-8), 65, 108
 1,3-CYCLOPENTADIENE, 1,2,3,4,5-PENTAMETHYL-, 65, 42
 2-CYCLOPENTEN-1-ONE, 3-METHYL-2-PENTYL-, 65, 26
 CYCLOPROPENONE 1,3-PROPANEDIOL KETAL: 4,8-DIOXASPIRO[2.5]OCT-1-ENE;
 (60935-21-9), 65, 32

1-DEOXY-2,3,4,6-TETRA-O-ACETYL-1-(2-CYANOETHYL)- α -D-GLUCOPYRANOSE:

D-GLYCERO-D-IDO-NONONONITRILE, 4,8-ANHYDRO-2,3-DIDEOXY-,

5,6,7,9-TETRAACETATE: (86563-27-1), 65, 236

DIALKOXYACETYLENES, 65, 68

Dibromomethane: Methane, dibromo-; (74-95-3), 65, 81

1,2-Di-tert-butoxy-1-chloroethene. (E)-: Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E); (70525-93-8), 65, 58

1,2-Di-tert-butoxy-1,2-dichloroethane, dl-: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy)]bis(oxy)bis[2-methyl-, (R^* , R^*)-(±)-; (68470-80-4), 65, 68

1,2-Di-tert-butoxy-1,2-dichloroethane, meso-: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy)]bis(oxy)]bis[2-methyl-, (R^* , S^*)-; (68470-81-5), 65, 68

2,3-Di-tert-butoxy-1,4-dioxane, cis-: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis-; (68470-78-0), 65, 68

2,3-Di-tert-butoxy-1,4-dioxane, trans-: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans-; (68470-79-1), 65, 68

DI-TERT-BUTOXYETHYNE: PROPANE, 2,2'-[1,2-ETHYNYEDIYLBIS(OXY)]BIS[2-METHYL-; (66478-63-5), 65, 68

2,3-Dichloro-1,4-dioxane, trans-: 1,4-Dioxane, 2,3-dichloro-, trans-; (3883-43-0), 65, 68

5,5-Dicyano-4-phenylcyclopent-2-enone 1,3-propanediol ketal:

6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-; (88442-12-0), 65, 32

Diethyl aminomethylphosphonate: Phosphonic acid, (aminomethyl)-, diethyl ester; (50917-72-1), 65, 119

DIETHYL N-BENZYLIDENEAMINOMETHYLPHOSPHONATE: PHOSPHONIC ACID,

[[(PHENYLMETHYLENE)AMINO]METHYL]-, DIETHYL ESTER;

(50917-73-2), 65, 119

Diethyl isocyanomethylphosphonate: Phosphonic acid, (isocyanomethyl)-, diethyl ester; (41003-94-5), **65**, 119

Diethyl oxalate: Oxalic acid, diethyl ester; Ethanedioic acid, diethyl ester; (95-92-1), **65**, 146

Diethyl phthalimidomethylphosphonate: Phosphonic acid, (phthalimidomethyl)-, diethyl ester; Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-methyl]-, diethyl ester; (33512-26-4), **65**, 119

DIHYDROJASMONE, **65**, 26

Diisopropylamine; 2-Propanamine, N-(1-methylethyl)-; (108-18-9), **65**, 98

DIISOPROPYL (2S,3S)-2,3-O-ISOPROPYLIDENETARTRATE: 1,3-DIOXOLANE-4,5-DICARBOXYLIC ACID, 2,2-DIMETHYL-, BIS(1-METHYLETHYL) ESTER, (4R-TRANS)-; (81327-47-1), **65**, 230

1,1-Dimethoxyethylene: Ethene, 1,1-dimethoxy-; (922-69-0), **65**, 98

4-(N,N-Dimethylamino)pyridine: Pyridine, 4-(dimethylamino)-; 4-Pyridinamine, N,N-dimethyl-; (1122-58-3), **65**, 12

Dimethyl diazomethylphosphonate: Phosphonic acid, (diazomethyl)-, dimethyl ester; (27491-70-9), **65**, 119

3,3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE: 1,5-PENTANEDIONE, 3,3-DIMETHYL-1,5-DIPHENYL-; (42052-44-8), **65**, 12

1,2-DIMETHYLENECYCLOHEXANE: CYCLOHEXANE, 1,2-DIMETHYLENE; CYCLOHEXANE, 1,2-BIS(METHYLENE)-; (2819-48-9), **65**, 90

Dimethyl (2S,3S)-2,3-O-isopropylidenetartrate: 1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester, (4R-trans)- or (4S-trans)-; (37031-29-1) or (37031-30-4), **65**, 230

Dimethyl methoxymethylenemalonate: Malonic acid, (methoxymethylene)-, dimethyl ester; Propanedioic acid, (methoxymethylene)-, dimethyl ester; (22398-14-7), **65**, 98

1,3-DIMETHYL-3-METHOXY-4-PHENYLAZETIDINONE: 2-AZETIDINONE, 3-METHOXY-
1,3-DIMETHYL-4-PHENYL-; (82918-98-7), **65**, 140

UMAP, **65**, 12

1,3-Dioxane, 2-(bromomethyl)-2-(chloromethyl)-, **65**, 32

1,4-Dioxane, 2,3-dichloro-, trans-, **65**, 68

1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans-, **65**, 68

1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis-, **65**, 68

6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-, **65**, 32

4,8-DIOXASPIRO[2.5]OCT-1-ENE, **65**, 32

p-Dioxino[2,3,-b]-p-dioxin, hexahydro, **65**, 68

[1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro, **65**, 68

1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester,
(4R-trans)- or (4S-trans)-, **65**, 230

1,3-DIOXOLANE-4,5-DICARBOXYLIC ACID, 2,2-DIMETHYL-, BIS(1-METHYLETHYL) ESTER,
(4R-TRANS)-, **65**, 230

2,7-DISILAOcta-3,5-DIYNE, 2,2,7,7-TETRAMETHYL-, **65**, 52

3,7-Dithianonane-1,9-diol: Ethanol, 2,2'-(trimethylenedithio)di-;
Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis-;
(16260-48-3), **65**, 150

3,7-Dithianonane-1,9-dithiol: Ethanethiol, 2,2'-(trimethylenedithio)di-;
Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis-; (25676-62-4). **65**, 150

Ethane, 1,1',1''-[methylidynetris(oxy)]tris-, **65**, 146

Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1), **65**, 17

Ethanedioic acid, diethyl ester, **65**, 146

Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis-, **65**, 150

Ethanethiol, 2,2'-(trimethylenedithio)di-, **65**, 150

Ethanol, 2-chloro-, 65, 150

Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis-, 65, 150

Ethanol, 2,2'-(trimethylenedithiol)di-, 65, 150

Ethanone, 1-phenyl-, 65, 6, 119

Ethene, 1,1-dimethoxy-, 65, 98

ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE: CYCLOHEXANEBUTANOIC ACID, γ -OXO-, ETHYL
ESTER; (54966-52-8), 65, 17

Ethyl ether, compd. with boron fluoride (BF_3) (1:1), 65, 17

Ethyl N-(2-methyl-3-nitrophenyl)formimidate, 65, 146

Ethylenediaminetetraacetic acid, tetrasodium salt: Glycine, N,N'-1,2-
ethanediylbis[N-(carboxymethyl)]-, tetrasodium salt, trihydrate;
(67401-50-7), 65, 166

Ethyne, 65, 61

Formic acid, chloro-, methyl ester, 65, 47

Glucopyranoside, methyl, α -D-, 65, 243

Glucopyranoside, methyl 4,6-O-benzylidene-, α -D-, 65, 243

GLUCOPYRANOSIDE, METHYL 6-BROMO-6-DEOXY, 4-BENZOATE, α -D-, 65, 243

Glucopyranoside, methyl 4,6-O-(phenylmethylene)-, α -D-, 65, 243

Glucopyranosyl bromide, 2,3,4,6-tetraacetate, α -D-, 65, 236

Glucopyranosyl bromide tetraacetate, α -D-, 65, 236

GLYCERO-D-IDO-NONONONITRILE, 4,8-ANHYDRO-2,3-DIDEOXY-, 5,6,7,9-TETRAACETATE,
 α -D-, 65, 236

Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)]-, tetrasodium salt,
trihydrate, 65, 166

2,5-Heptadien-4-ol, 3,4,5-trimethyl-, 65, 42

Heptanal; (111-71-7), 65, 26

3-HEPTANONE, 4-METHYL-, (S)-, 65, 183

HEXAHYDRO-4,4,7-TRIMETHYL-4H-1,3-BENZOXATHIIN: 4H-1,3-BENZOXATHIIN.

HEXAHYDRO-4,4,7-TRIMETHYL-; (59324-06-0), 65, 215

Hydrazine, (1,1-dimethylethyl)-, monohydrochloride, 65, 166

Hydrazine, tert-butyl, monohydrochloride, 65, 166

Hydrogen peroxide; (7722-84-1), 65, 166

3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE: 1-BUTANONE,

3-HYDROXY-3-METHYL-1-PHENYL-; (43108-74-3), 65, 6, 12

N-Hydroxymethylphthalimide: Phthalimide, N-(hydroxymethyl)-;

1H-Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)- (118-29-6), 65, 119

INDOLE, 4-NITRO-, 65, 146

INVERSE ELECTRON DEMAND DIELS-ALDER, 65, 98

6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine,

N-[(2-iodo-4,5-dimethoxyphenyl)methylene]-; (61599-78-8), 65, 108

Isoindole-1,3-(2H)-dione, 2-(bromomethyl)-, 1H-, 65, 119

Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)-, 1H-, 65, 119

Isomenthol, (+)-: Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2 β ,5 β)]-;

(23283-97-8), 65, 81

Isomenthone, (+)-: Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)-;

(1196-31-2), 65, 81

Isopropyl alcohol, titanium (4+) salt, 65, 230

Isopropylideneacetophenone: 2-Buten-1-one, 3-methyl-1-phenyl-;

(5650-07-7), 65, 12

β -Lactams, 65, 140

Lead dioxide: Lead oxide; (1309-60-0), 65, 166

Lead oxide, 65, 166

Lithiobutadiyne, 65, 52

Lithium, butyl-, 65, 98, 108, 119

Lithium diisopropylamide, 65, 98

Lithium, methyl-, 65, 47, 140

MACROCYCLIC SULFIDES, 65, 150

Malonic acid, (methoxymethylene)-, dimethyl ester, 65, 98

Malononitrile, benzylidene-, 65, 32

p-MENTH-4-(8)-EN-3-ONE, (R)-(+)-, 65, 203, 215

2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol: Cyclohexanol-2-(1-mercapto-1-methylethyl)-5-methyl-, [1R-(1 α ,2 α ,5 α)]-; (79563-68-1); [1R-(1 α ,2 β ,5 α)]-; (79563-59-0); [1S-(1 α ,2 α ,5 β)]-; (79563-67-0), 65, 215

Methanamine, N-(phenylmethylene)-, 65, 140

Methane, dibromo-, 65, 81

METHANESULFONYL BROMIDE, BROMO-, 65, 90

N¹N²-Bis(methoxycarbonyl)sulfur diimide: Sulfur diimide, dicarboxy-, dimethyl ester; (16762-82-6), 65, 159

6-Methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene: 2-Naphthalene-carboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester; (78112-34-2), 65, 98

Methylamine, N-benzylidene-, 65, 140

METHYL 4-O-BENZOYL-6-BROMO-6-DEOXY- α -D-GLUCOPYRANOSIDE:

GLUCOPYRANOSIDE, METHYL 6-BROMO-6-DEOXY, 4-BENZOATE,
 α -D-; (10368-81-7), 65, 243

Methyl 4,6-O-benzylidene- α -D-glucopyranoside: Glucopyranoside, methyl 4,6-O-benzylidene- α -D-; α -D-glucopyranoside, methyl 4,6-O-(phenylmethylene)-; (3162-96-7), 65, 243

N-Methylbenzylideneimine: Methylamine, N-benzylidene-; Methanamine, N-(phenylmethylene)-; (622-29-7), 65, 140

2-Methyl-2-butene: 2-Butene, 2-methyl-; (513-35-9), 65, 159

Methyl carbamate: Carbamic acid, methyl ester; (598-55-0), 65, 159

METHYL 4-CHLORO-2-BUTYNOATE: 2-BUTYNOIC ACID, 4-CHLORO-, METHYL ESTER;
(41658-12-2), 65, 47

Methyl chloroformate: Formic acid, chloro-, methyl ester;
Carbonochloridic acid, methyl ester; (79-22-1), 65, 47

1-Methylcyclohexene: Cyclohexene, 1-methyl-; (591-49-1), 65, 90

Methyl N,N-dichlorocarbamate: Carbamic acid dichloro-, methyl ester;
(16487-46-0), 65, 159

Methyl α -D-glucopyranoside: Glucopyranoside, methyl, α -D-;
 α -D-glucopyranoside, methyl; (97-30-3), 65, 243

4-METHYL-3-HEPTANONE, (S)-(+) -: 3-HEPTANONE, 4-METHYL-, (S)-;
(51532-30-0), 65, 183

4-Methyl-3-heptanone SAMP-hydrazone, (S)-(+) -: 1-Pyrrolidinamine,
N-(1-ethyl-2-methylpentylidene)-2-(methoxymethyl)-,
[S-[R^{*}, R^{*}-(Z)]-; (69943-24-4), 65, 183

Methyl lithium: Lithium, methyl-; (917-54-4), 65, 47, 140

[(Methyl)(methoxy)carbene]pentacarbonyl chromium(0): Chromium,
pentacarbonyl(1-methoxyethylidene)-, (OC-6-21)-; (20540-69-6), 65, 140

METHYL N-(2-METHYL-2-BUTENYL)CARBAMATE: CARBAMIC ACID, (2-METHYL-2-BUTENYL)-, METHYL ESTER; (86766-65-6), **65**, 159

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (2R,5R)-: Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)-; (57707-92-3), **65**, 203

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (2S,5R)-: Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)-; (65337-06-6), **65**, 203

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate, (1R,2S,5R)-: Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester. [1R-(1 α ,2 β ,5 α)]-; (71804-27-8), **65**, 203

5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone, cis- and trans-; **65**, 215

5-Methyl-2-(1-methyl-1-thioethyl)cyclohexanol. **65**, 215

2-Methyl-3-nitroaniline: o-Toluidine, 3-nitro-; Benzeneamine, 2-methyl-3-nitro-; (603-83-8), **65**, 146

METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2H-1-BENZOPYRAN-3-CARBOXYLATE: 2H-1-BENZOPYRAN-3-CARBOXYLIC ACID, 5,6,7,8-TETRAHYDRO-2-OXO-, METHYL ESTER; (85531-80-2), **65**, 98

3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE: 2-CYCLOPENTEN-1-ONE, 3-METHYL-2-PENTYL-; (1128-08-1), **65**, 26

2-METHYL-2-PHENYL-4-PENTENAL: 4-PENTENAL, 2-METHYL-2-PHENYL-; (24401-39-6), **65**, 119

METHYLENATION OF CARBONYL COMPOUNDS, **65**, 81

3-METHYLENE-CIS-P-MENTHANE, (+)-: (CYCLOHEXANE, 5-METHYL-1-METHYLENE-2-(1'-METHYLETHYL)-, R,R-), **65**, 81

Proline, D-; (344-25-2), **65**, 173
 Proline, L-; (147-85-3), **65**, 173
 2-Propanamine, N-(1-methylethyl)-, **65**, 98
 Propane, 1-bromo-3-chloro-2,2-dimethoxy-, **65**, 32
 Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E)-, **65**, 68
 Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy1)]bis(oxy)bis[2-methyl-,
 (R*,R*)-(±)-, **65**, 68
 Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy1)bis(oxy)]bis[2-methyl-,
 (R*,S*)-, **65**, 68
 PROPANE, 2,2'-[1,2-ETHYNYDIYLBIS(OXY)]BIS[2-METHYL-, **65**, 68
 1,3-Propanediamine, **65**, 224
 Propanedinitrile, (phenylmethylene)-, **65**, 32
 Propanedioic acid, (methoxymethylene)-, dimethyl ester, **65**, 98
 1,3-Propanediol; (504-63-2), **65**, 32
 1,3-Propanedithiol; (109-80-8). **65**, 150
 2-Propanol, titanium (4+) salt, **65**, 230
 2-Propanone, 1-bromo-3-chloro-, dimethyl acetal, **65**, 32
 PROPARGYL CHLORIDE: PROPYNE, 3-CHLORO-; 1-PROPYNE, 3-CHLORO-;
 (624-65-7), **65**, 47
 1-Propen-1-amine, 2-phenyl-N-(phenylmethylene)-, **65**, 119
 2-Propenenitrile, **65**, 236
 1-PROPYNE, 3-CHLORO-, **65**, 47
 PULEGONE, (+): p-MENTH-4-(8)-EN-3-ONE, (R)-(+)-; CYCLOHEXANONE,
 5-METHYL-2-(1-METHYLETHYLIDENE)-, (R)-; (89-82-7), **65**, 203, 215
 4-Pyridinamine, N,N-dimethyl-, **65**, 12
 Pyridine, 4-(dimethylamino)-, **65**, 12

1-Pyrrolidinamine, N-(1-ethyl-2-methylpentylidene)-2-(methoxymethyl)-, [S-[R^{*},R^{*}-(Z)]-, 65, 183

1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)-, 65, 183

1-Pyrrolidinamine, 2-(methoxymethyl)-, (R)-(+)-, (72748-99-3), 65, 173

1-Pyrrolidinamine, 2-(methoxymethyl)-, (S)-(-)-, (59983-30-0), 65, 173, 183

Pyrrolidine, 2-(methoxymethyl)-, (S)-(+)-, (63126-47-6), 65, 173

Pyrrolidine, 2-(methoxymethyl)-1-nitroso-, (S)-, 65, 183

1-Pyrrolidinecarboxaldehyde, 2-(hydroxymethyl)-, (S)-(-)-, (55456-46-7), 65, 173

1-Pyrrolidinecarboxaldehyde, 2-(methoxymethyl)-, (S)-(-)-, (63126-45-4), 65, 173

2,5-PYRROLIDINEDIONE, 1-BROMO-, 65, 243

2-Pyrrolidinemethanol, (S)-(+)-, (23356-96-9), 65, 173

Ramberg-Bäcklund reaction, 65, 90

RAMP: (R)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine, 2-(methoxymethyl)-, (R)-, 65, 173, 183

RING EXPANSION, 65, 17

SAMP: (S)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine, 2-(methoxymethyl)-, (S)-, (59983-39-0), 65, 173, 183

SILANE, 1,3-BUTADIYNE-1,4-DIYLBIS[TRIMETHYL-, 65, 52

Silane, chlorotrimethyl-, 65, 61, 1

Silane, (1-cyclobuten-1,2-ylenedioxy)bis[trimethyl-, 65, 17

Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl-, 65, 17

Silane, ethynyltrimethyl-, 65, 52, 61

SILANE, (ISOPROPENYLOXY)TRIMETHYL, 65, 1

2-Naphthalenecarboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester, **65**, 98

4-NITROINDOLE: INDOLE, 4-NITRO-; (4769-97-5), **65**, 146

1-Nitroso-2-methoxymethylpyrrolidine. (S)-: Pyrrolidine. 2-(methoxymethyl)-1-nitroso-, (S)-; (60096-50-6), **65**, 183

Nitroso-tert-octane: Pentane, 2,2,4-trimethyl-4-nitroso-; (31044-98-1), **65**, 166

tert-Octylamine: 2-Pentanamine, 2,4,4-trimethyl-; (107-45-9), **65**, 166

N-tert-Octyl-O-tert-butylhydroxylamine: 2-Pentanamine. N-(1,1-dimethylethoxy)-2,4,4-trimethyl-; (68295-32-9), **65**, 166

Orthoformic acid, triethyl ester, **65**, 146

Oxalic acid, diethyl ester, **65**, 146

1,3-OXATHIANE, **65**, 215

Oxonium, trimethyl-, tetrafluoroborate (1-), **65**, 140

Ozone (10028-15-6), **65**, 183

Paraformaldehyde: Poly(oxymethylene); (9002-81-7), **65**, 215

1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE: 1,3-CYCLOPENTADIENE. 1,2,3,4,5-PENTAMETHYL-; (4045-44-7), **65**, 42

2-Pentanamine, N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-2,4,4-trimethyl-, **65**, 166

2-Pentanamine, N-(1,1-dimethylethoxy)-2,4,4-trimethyl-, **65**, 166

2-PENTANAMINE, N-(1,1-DIMETHYLETHYL)-2,4,4-TRIMETHYL-, **65**, 166

2-Pentanamine, 2,4,4-trimethyl-, **65**, 166

1,5-PENTANEDIONE, 3,3-DIMETHYL-1,5-DIPHENYL-, **65**, 12

Pentane, 2,2,4-trimethyl-4-nitroso-, **65**, 166

3-Pentanone SAMP-hydrazone: 1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)-; (59983-36-7), **65**, 183

4-PENTENAL, 2-METHYL-2-PHENYL-, **65**, 119

8-PHENYLMENTHOL, (-)-: CYCLOHEXANOL, 5-METHYL-2-(1-METHYL-1-PHENYLETHYL)-, [1R-(1 α ,2 β ,5 α)]-; (65253-04-5), **65**, 203

2-Phenyl-N-(phenylmethylene)-1-propen-1-amine: 1-Propen-1-amine, 2-phenyl-N-(phenylmethylene)-; (64244-34-4), **65**, 119

1-Phenyl-1-trimethylsiloxyethylene: Silane, trimethyl[(1-phenylvinyl)oxy]-; Silane, trimethyl[(1-phenylethenyl)oxy]-; (13/35-81-4), **65**, 6

Phosphonic acid, (aminomethyl), diethyl ester, **65**, 119

Phosphonic acid, (diazomethyl)-, dimethyl ester, **65**, 119

Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]-, diethyl ester, **65**, 119

Phosphonic acid, (isocyanomethyl)-, diethyl ester, **65**, 119

PHOSPHONIC ACID [[(PHENYLMETHYLENE)AMINO]METHYL]-, DIETHYL ESTER, **65**, 119

Phosphonic acid, (phthalimidomethyl)-, diethyl ester, **65**, 119

Phosphorodichloridic acid, 2-chloroethyl ester, **65**, 68

Phosphorous acid, triethyl ester, **65**, 108, 119

Phthalimide, N-(bromoethyl)-, **65**, 119

Phthalimide, N-(hydroxymethyl)-, **65**, 119

PINENE, (-)- α -: 2-PINENE, (1S,5S)-(-); BICYCLO[3.1.1]HEPT-2-ENE, 2,6,6-TRIMETHYL-, (1S)-; (7785-26-4), **65**, 224

PINENE, (-)- β -: BICYCLO[3.1.1]HEPTANE, 6,6-DIMETHYL-2-METHYLENE-, (1S)-; (18172-67-3), **65**, 224

Poly(oxymethylene), **65**, 215

Potassium 3-aminopropylamide (KAPA), **65**, 224

Potassium hydride; (7693-26-7), **65**, 224

SILANE, TRIMETHYL[(1-METHYLETHENYL)OXY]-, **65**, 1

Silane, trimethyl[(1-phenylethyl)oxy]-, **65**, 6, 12

Silane, trimethyl[(1-phenylvinyl)oxy]-, **65**, 6, 12

Sodium naphthalenide, **65**, 166

Sodium tungstate dihydrate: Tungstic acid, disodium salt, dihydrate;
(10213-10-2), **65**, 166

SPIRO[4.5]DECAN-1,4-DIONE; (39984-92-4), **65**, 17

Stannane, tetrachloro-, **65**, 17

Stannane, tributyl-, **65**, 236

STETTER REACTION, **65**, 26

SUCCINIMIDE, N-BROMO-, **65**, 243

Sulfur chloride, **65**, 159

Sulfur dichloride: Sulfur chloride; (10545-99-0), **65**, 159

Sulfur diimide, dicarboxy-, dimethyl ester, **65**, 159

Sulfonyl chloride isocyanate, **65**, 135

2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide: Glucopyranosyl bromide
tetraacetate, α -D-; α -D-glucopyranosyl bromide, 2,3,4,6-tetraacetate;
(572-09-8), **65**, 236

Tetraisopropyl titanate: Isopropyl alcohol, titanium (4+) salt;
2-Propanol, titanium (4+) salt; (546-68-9), **65**, 230

4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE:
[1,1'-BIPHENYL]-2,2'-DICARBOXALDEHYDE, 4,4',5,5'-TETRAMETHOXY-;
(29237-14-7), **65**, 108

2,5,7,10-Tetraoxabicyclo[4.4.0]decane, cis-: p-Dioxino[2,3,-b]-p-dioxin,
hexahydro-; [1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro;
(4362-05-4), **65**, 68

1,4,8,11-TETRATHIACYCLOTETRADECANE: (24194-61-4), 65, 150

Thiourea: Urea, thio-, (62-56-6), 65, 150

Tin chloride, 65, 17

Tin tetrachloride: Tin chloride; Stannane, tetrachloro-, (7646-78-8), 65, 17

Titanium chloride, 65, 81, 6

Titanium tetrachloride: Titanium chloride; (7550-45-0), 65, 81, 6

α -Toluenethiol, 65, 215

o-Toluidine, 3-nitro-, 65, 146

Transesterification, 65, 230

Tributyltin hydride: Stannane, tributyl-, (688-73-3), 65, 236

Triethyl orthoformate: Orthoformic acid, triethyl ester; Ethane, 1,1',1''-[methylidynetris(oxy)]tris-, (122-51-0), 65, 146

Triethyl phosphite: Phosphorous acid, triethyl ester; (122-52-1), 65, 119, 108

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride; (407-25-0), 65, 12

3,4,5-Trimethyl-2,5-heptadien-4-ol: 2,5-Heptadien-4-ol, 3,4,5-trimethyl-, (64417-15-8), 65, 42

Trimethyloxonium tetrafluoroborate: Oxonium, trimethyl-, tetrafluoroborate (1-); (420-37-1), 65, 140

TRIMETHYLSILYLACETYLENE: SILANE, ETHYNYLTRIMETHYL-, (1066-54-2), 65, 52, 61

Trithiane, Sym-: S-Trithiane; 1,3,5-Trithiane; (291-21-4), 65, 90

Tungstic acid, disodium salt, dihydrate, 65, 166

ULLMANN REACTION, 65, 108

2,5-Undecanedione; (7018-92-0), 65, 26

Urea, thio-, 65, 150

Vibro-mixer, 65, 52

Vinyl acetate: Acetic acid vinyl ester; Acetic acid ethenyl ester;
(108-05-4), 65, 135

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CONTENTS

Rick L. Danheiser, Yeun-Min Tsai, and David M. Fink	1	A GENERAL METHOD FOR THE SYNTHESIS OF ALLENYLSILANES: 1-METHYL-1- (TRIMETHYLSILYL)ALLENE
Rick L. Danheiser, David M. Fink, and Yeun-Min Tsai	8	A GENERAL [3+2] ANNULATION: CIS-4- EXO-ISOPROPENYL-1,9-DIMETHYL-8- (TRIMETHYLSILYL)BICYCLO[4.3.0]NON- 8-EN-2-ONE
Rick L. Danheiser, David M. Fink, Kazuo Okano, Yeun-Min Tsai, and Steven W. Szczepanski	14	(1-OXO-2-PROPENYL)TRIMETHYLSILANE
S. Tsuboi, T. Masuda, S. Mimura, and A. Takeda	22	ETHYL (E,Z)-2,4-DECADIENOATE
Dennis F. Vogel and George H. Ruchi	29	α -UNSUBSTITUTED γ,δ -UNSATURATED ALDEHYDES BY CLAISEN REARRANGEMENT: 3-PHENYL-4-PENTENAL
Dietrich Spitzner and Anita Engler	37	APROTIC DOUBLE MICHAEL ADDITION: PREPARATION OF 1,3-DIMETHYL-5- OXOBICYCLO[2.2.2]OCTANE-2- CARBOXYLIC ACID
Hiichi Nakamura and Isao Kuwajima	43	COPPER-CATALYZED CONJUGATE ADDITION OF A ZINC HOMOENOLATE: ETHYL 3-[3-(TRIMETHYLSILOXY)CYCLOHEX- 2-ENYL]]PROPIONATE
William A. Nugent and Frank W. Hobbs, Jr.	52	CONJUGATE ADDITION/CYCLIZATION OF A CYANOCUPRATE: 2-CARBOMETHOXY- 3-VINYLCYCLOPENTANONE
Ei-ichi Negishi, Tamotsu Takahashi, and Shigeru Baba	60	PALLADIUM-CATALYZED SYNTHESIS OF CONJUGATED DIENES: (5Z,7E)-5,7-HEXADECADIENE
Ei-ichi Negishi, Tamotsu Takahashi, and Anthony O. King	67	SYNTHESIS OF BIARYLS VIA PALLADIUM- CROSS COUPLING: 2-METHYL-4'-NITROBIPHENYL
Robert Mook, Jr. and Philip Michael Sher	75	VINYL RADICAL CYCLIZATION VIA ADDITION OF TIN RADICALS TO TRIPLE BONDS
Isao Kuwajima and Hirokazu Urabe	87	CYCLOPENTANONES FROM CARBOXYLIC ACIDS VIA INTRAMOLECULAR ACYLATION OF ALKYLSILANES: 2-METHYL-2-VINYLCYCLOPENTANONE

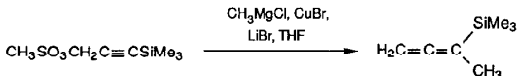
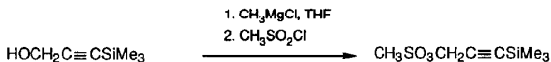
Tony C. T. Chang, Myron Rosenblum, and Nancy Simms	95	VINYLATION OF ENOLATES WITH A VINYL CATION EQUIVALENT: <i>trans</i> -3-METHYL- 2-VINYLCYCLOHEXANONE
Christina M. J. Fox and Steven V. Ley	108	PREPARATION OF <i>tert</i> -BUTYL ACETOTHIOACETATE AND USE IN THE SYNTHESIS OF 3-ACETYL-4-HYDROXY- 5,5-DIMETHYLFURAN-2(5H)-ONE
Tamotsu Fujisawa and Toshio Sato	116	KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS: METHYL 6-OXODECANOATE
Tamotsu Fujisawa and Toshio Sato	121	REDUCTION OF CARBOXYLIC ACIDS TO ALDEHYDES: 6-OXODECANAL
Suzanne R. Abrams and Angela C. Shaw	127	TRIPLE BOND ISOMERIZATIONS: 2- TO 9-DECYN-1-OL
Merrick K. Almond, Julie B. Stimmel, E. Alan Thompson, and G. Marc Loudon	132	HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS USING [1,1-BIS(TRIFLUOROACETOXY)]- IODOBENZENE: CYCLOBUTYLAMINE HYDROCHLORIDE FROM CYCLOBUTANECARBOXAMIDE
Dale L. Boger, James S. Panek, and Masami Yasuda	142	PREPARATION AND INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF AN ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: TRIETHYL 1,2,4-TRIAZINE- 3,5,6-TRICARBOXYLATE
Bernhard Koppenhoefer and Volker Schurig	151	(<i>S</i>)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY FROM (<i>S</i>)-2- AMINO ACIDS: (<i>S</i>)-2-CHLOROPROPANOIC ACID
Bernhard Koppenhoefer and Volker Schurig	160	(<i>R</i>)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY FROM (<i>S</i>)-2- CHLOROALKANOIC ACIDS VIA (<i>S</i>)-2- CHLORO-1-ALKANOLS: (<i>R</i>)-METHYLOXIRANE
Osmo Hormi	173	UTILIZATION OF β -CHLORO ALKYLIDENE/ARYLIDENE MALONATES IN ORGANIC SYNTHESIS: SYNTHESIS OF ETHYL CYCLOPROPYLPROPIOLATE
Donald Bankston	180	OXIDATIVE CLEAVAGE OF AN AROMATIC RING: <i>cis,cis</i> -MONOMETHYL MUCONATE FROM 1,2-DIHYDROXYBENZENE

Keiji Maruoka, Shuichi Nakai, and Hisashi Yamamoto	185	PREPARATION OF 2-PROPYL-1- AZACYCLOHEPTANE FROM CYCLOHEXANONE OXIME
Robert K. Boeckman, Jr., Robert B. Perni, James E. Macdonald, and Anthony J. Thomas	194	6-DIETHYLPHOSPHONOMETHYL-2,2- DIMETHYL-1,3-DIOXEN-4-ONE
Lal C. Vishwakarma, Orum D. Stringer, and Franklin A. Davis	203	(±)-trans-2-(PHENYLSULFONYL)-3- PHENYLOXAZIRIDINE
Andrew B. Woodside, Zheng Huang, and C. Dale Poulter	211	TRISAMMONIUM GERANYL DIPHOSPHATE
J. Villieras and M. Rambaud	220	ETHYL α -(HYDROXYMETHYL)ACRYLATE
Unchecked Procedures	225	
Cumulative Author Index for Volumes 65 and 66	228	
Cumulative Subject Index for Volumes 65 and 66	230	

A GENERAL METHOD FOR THE SYNTHESIS OF ALLENYLSILANES:

1-METHYL-1-(TRIMETHYLSILYL)ALLENE

(Silane, trimethyl(1-methyl-1,2-propadienyl)-)



Submitted by Rick L. Danheiser, Yeun-Min Tsai, and David M. Fink.¹

Checked by Marianne Marsi and Bruce E. Smart.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum, low temperature thermometer, and a 250-mL pressure-equalizing dropping funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 30.0 g (0.234 mol) of 3-trimethylsilyl-2-propyn-1-ol (Note 2) and 230 mL of dry tetrahydrofuran (Note 3), and then cooled with an ice bath while 84 mL of a 2.8 M solution of methylmagnesium chloride in tetrahydrofuran (Note 4) is added at such a rate that the internal temperature does not rise above 10°C. Approximately 1.5 hr is required for the addition, after which time the gray solution is stirred at 0°C for 30 min, and then cooled below -70°C with a dry ice-acetone bath. Methanesulfonyl chloride (26.8 g, 0.234 mol) (Note 5) is added over 10 min via syringe, and after 30 min the cold bath is removed and the pale yellow reaction mixture is allowed to warm to room temperature over 2 hr.

A 2-L, three-necked, round-bottomed flask equipped with a vacuum adapter and two glass stoppers (Note 1) is charged with 21.4 g (0.246 mol) of anhydrous lithium bromide and 35.3 g (0.246 mol) of anhydrous cuprous bromide (Note 6). The reaction vessel is evacuated and the contents are briefly heated with a Bunsen burner flame. After 30 min the vacuum is replaced by nitrogen and the apparatus is equipped with a mechanical stirrer and two rubber septa. Dry tetrahydrofuran (260 mL) (Note 3) is added, and the resulting green solution containing a small amount of undissolved solid is cooled with an ice bath while 84 mL of a 2.8 M solution of methylmagnesium chloride in tetrahydrofuran (Note 4) is added rapidly via syringe over 1-2 min. After 20 min of further stirring at 0°C, the reaction mixture appears as a viscous yellow-green suspension. The solution of the mesylate derivative of 3-trimethylsilyl-2-propyn-1-ol prepared above is now transferred via cannula over 45 min to the reaction mixture, which is cooled below -70°C with a dry ice-acetone bath. After 30 min, the cold bath is removed and the green reaction mixture is stirred at room temperature for 2 hr. The blue-gray mixture is then poured into a 2-L Erlenmeyer flask containing a magnetically stirred mixture of 400 mL of pentane, 200 mL of water, and 400 mL of saturated ammonium chloride solution. The organic phase is separated and washed successively with two 200-mL portions of saturated ammonium chloride solution, ten 1-L portions of water (Note 7), and 100 mL of saturated sodium chloride solution. The organic phase is dried over anhydrous sodium sulfate, and the drying agent is removed by filtration. The solvent is removed from the filtrate by atmospheric distillation through a 10-cm Vigreux column. The residual liquid is carefully distilled through a 12-cm column packed with glass helices to give 21.3-22.2 g, (72-75%) of 1-methyl-1-(trimethylsilyl)-allene as a colorless liquid, bp 111°C (Notes 8-11).

2. Notes

1. The apparatus is flame-dried at 20 mm pressure and then maintained under an atmosphere of nitrogen during the course of the reaction.

2. 3-Trimethylsilyl-2-propyn-1-ol was obtained from Petrarch Systems, Inc. and used as received. Alternatively, it can be prepared by the silylation of 2-propyn-1-ol.²

3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

4. Methylmagnesium chloride in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc.

5. Methanesulfonyl chloride was obtained from the Aldrich Chemical Company, Inc. and purified by distillation from phosphorus pentoxide before use.

6. Lithium bromide, obtained from Aldrich Chemical Company, Inc., and cuprous bromide, supplied by Fluka Chemical Corporation, were dried at 120°C (0.02 mm) for 8 hr before use. The checkers obtained lower yields (54-58%) with cuprous bromide that was supplied by other commercial sources.

7. This procedure conveniently removes tetrahydrofuran from the organic phase.

8. The submitters report bp 112-113°C and state that an additional 2.2 g (7%) of product, bp 54-56°C (90 mm), can be obtained by combining the distillation forerun with the pot residue and redistilling the mixture at reduced pressure.

9. The allenylsilane thus obtained was found by ^1H NMR analysis to be contaminated with 7-8% of 1-trimethylsilyl-1-butyne. This material is suitable for use in [3+2] annulations.³ Efficient stirring during the formation of the mixed cuprate reagent is important in minimizing the amount of this impurity produced in the reaction.

10. The submitters note that if pure 1-methyl-1-(trimethylsilyl)allene is required, the mixture of allenylsilane and 1-trimethylsilyl-1-butyne is treated with 0.15 equiv of silver nitrate in 10:1 methanol-water at room temperature for 1 hr. Extraction with pentane and distillation furnishes the allenylsilane in 79% yield. Gas chromatographic analysis (0.2 mm x 10.5 m methyl silicone-coated fused silica capillary column, split ratio 100:1, column pressure 20 psi, temperature 20°C) indicates that this material contains none of the acetylenic side product.

11. The product exhibits the following spectral properties: IR (neat) cm^{-1} : 2955, 2920, 2900, 2860, 1936, 1440, 1400, 1250, 936, 880, 830, 805, 750, and 685; ^1H NMR (250 MHz, CDCl_3) δ : 0.08 (s, 9 H), 1.67 (t, 3 H, $J = 3.3$), and 4.25 (q, 2 H, $J = 3.3$); ^{13}C NMR (67.9 MHz, CDCl_3) δ : -2.1, 15.1, 67.3, 69.1, and 209.1. The impurity, 1-trimethylsilyl-1 butyne, displays ^1H NMR peaks at 0.14 (s, 9 H), 1.15 (t, 3 H, $J = 7$), and 2.23 (q, 2 H, $J = 7$).

3. Discussion

Allenylsilanes serve as valuable three-carbon components in a general [3+2] annulation method for the synthesis of five-membered rings.⁴ A variety of general synthetic approaches to allenylsilanes have recently been developed,⁵⁻⁷ and a number of specialized routes to various specific functionalized derivatives⁸ are available as well. The present procedure

involves a modification of the general method of Vermeer,^{5a} which is the most widely applicable route to substituted allenylsilanes. Advantages of this approach include its efficiency, high regioselectivity, and utility in the synthesis of a variety of mono-, di-, and trisubstituted allenylsilane derivatives.

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
2. Komarov, N. V.; Shostakovskii, M. F. *Izvest. Akad. Nauk, S.S.S.R. Otdel. Khim. Nauk* **1960**, 1300; *Chem. Abstr.* **1961**, 55, 358g.
3. See Danheiser, R. L.; Fink, D. M.; Tasi, Y.-M. *Org. Synth.* **1988**, 66, 8.
4. (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, 103, 1604; (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, 39, 935.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

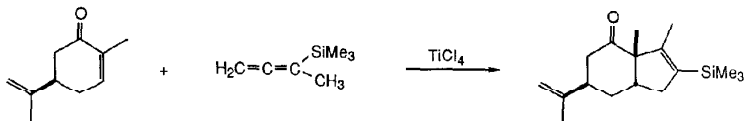
1-Methyl-1-(trimethylsilyl)allene: Silane, trimethyl(1-methyl-1,2-propadienyl)- (10); (74542-82-8)

3-Trimethylsilyl-2-propyn-1-ol: 2-Propyn-1-ol, 3-(trimethylsilyl)- (9); (5272-36-6)

A GENERAL [3+2] ANNULATION: CIS-4-EXO-ISOPROPENYL-

1,9-DIMETHYL-8-(TRIMETHYLSILYL)BICYCLO[4.3.0]NON-8-EN-2-ONE

(4H-Inden-4-one, 1,3a,5,6,7,7a-hexahydro-3,3a-dimethyl-6-(1-methylethenyl)-2-(trimethylsilyl)-, (3a α ,6 α ,7a α)-)



Submitted by Rick L. Danheiser, David M. Fink, and Yeun-Min Tsai.¹

Checked by Marianne Marsi and Bruce E. Smart.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a 25-mL pressure-equalizing dropping funnel, a mechanical stirrer, and a Claisen adapter fitted with a nitrogen inlet adapter and a low temperature thermometer (Note 1). The flask is charged with 11.5 g (0.077 mol) of (R)-(-)-carvone (Note 2), 10.8 g (0.079 mol) of 1-methyl-1-(trimethylsilyl)allene (Note 3), and 180 mL of dry dichloromethane (Note 4), and then cooled below -75°C with a dry ice-acetone bath while a solution of 17.4 g (0.092 mol) of titanium tetrachloride (Note 5) in 10 mL of dichloromethane is added dropwise over 1 hr. After 30 min, the cold bath is removed, and the reaction mixture, which appears as a red suspension, is allowed to warm to 0°C over approximately 30 min. The resulting dark red solution is poured slowly into a 2-L Erlenmeyer flask containing a magnetically-stirred mixture of 400 mL of diethyl ether and 400 mL of water (Note 6). The aqueous phase is separated and extracted with

two 200-mL portions of ether. The combined organic phases are washed with 250 mL of water and 250 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated at reduced pressure using a rotary evaporator. The residual yellow liquid is distilled through a 15-cm Vigreux column at reduced pressure to afford 17.5 g (82%) of the bicyclonononene **1** as a very pale yellow liquid, bp 98-101°C (0.03 mm). $[\alpha]_D^{20}$ -157.8 \pm 0.8 (1.57, CH₂Cl₂) (Notes 7 and 8).

2. Notes

1. The apparatus is flame-dried under vacuum and then maintained under an atmosphere of nitrogen during the course of the reaction.

2. (R)-(-)-Carvone was purchased from Aldrich Chemical Company, Inc. and distilled before use.

3. 1-Methyl-1-(trimethylsilyl)allene (90% purity, contaminated with 10% 1-trimethylsilyl-1-butyne) was prepared by the method of Danheiser, R. L.; Tsai, Y. M.; Fink, D. M. *Org. Synth.* **1988**, *66*, 1.

4. Dichloromethane was distilled from calcium hydride immediately before use.

5. Titanium tetrachloride (99.9%) was obtained from the Aldrich Chemical Company, Inc. and distilled before use. Lower yields (70-77%) resulted if the titanium tetrachloride was not distilled. Unreacted carvone is recovered if a small excess of titanium tetrachloride is not used.

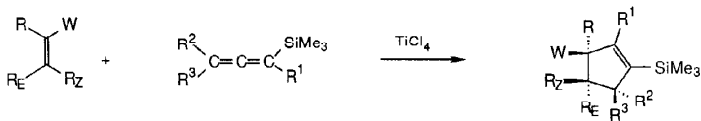
6. The two-phase mixture is vigorously stirred using a 7-cm Teflon-coated magnetic stirring bar.

7. The submitters report obtaining 18.8 g (88%) of product, bp 93-96°C (0.03 mm). The purity of the product was determined to be >99% by gas chromatographic analysis (10% OV 101 on 100-120 mesh Chromosorb W, 6 ft x 1/8 in, program: 200°C for 2 min and then 200-300°C at 32°C/min).

8. The product exhibits the following spectral properties: IR (neat) cm^{-1} : 3080, 2950, 2920, 1700, 1640, 1610, 1440, 1375, 1315, 1245, 1200, 830, 755, 680; ^1H NMR (250 MHz, CDCl_3) δ : 0.08 (s, 9 H), 1.10 (s, 3 H), 1.65 (t, 3 H, $J = 2.2$), 1.68 (m, 3 H), 1.65-1.72 (m, 2 H), 2.10 (d of m, 1 H, $J = 12.4$), 2.15-2.25 (m, 1 H), 2.27-2.31 (m, 2 H), 2.45-2.57 (m, 2 H), 4.63 (m, 1 H), 4.72 (m, 1 H); ^{13}C NMR (62.8 MHz, CDCl_3) δ : -0.7, 14.4, 21.1, 21.3, 32.4, 39.8, 42.0, 43.9, 46.1, 64.8, 110.4, 136.1, 147.7, 151.5, 215.6.

3. Discussion

The procedure described here serves to illustrate a general [3+2] annulation method² for the synthesis of cyclopentane derivatives. A unique feature of this one-step annulation is its capacity to generate regio-specifically five-membered rings substituted at each position, and functionally equipped for further synthetic elaboration. As formulated in the following equation, the reaction proceeds with remarkably high stereo-selectivity via the effective suprafacial addition of the three-carbon allene component to an electron-deficient olefin ("allenophile").


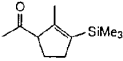

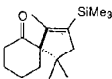

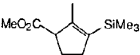

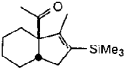

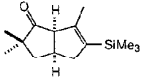

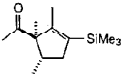

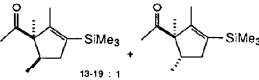

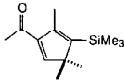

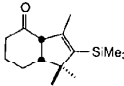


Some representative examples of the [3+2] annulation are listed in Table I. Both cyclic and acyclic allenophiles participate in the reaction. α -Alkylidene ketones undergo annulation to provide access to spiro-fused systems, and acetylenic allenophiles react to form cyclopentadiene derivatives. The reactions of (E)- and (Z)-3-methyl-3-penten-2-one illustrate the stereochemical course of the annulation, which proceeds with a strong preference for the suprafacial addition of the allene to the two-carbon allenophile. The high stereoselectivity displayed by the reaction permits the stereocontrolled synthesis of a variety of mono- and polycyclic systems.

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
2. (a) Danheiser, R. L.; Carini, D. J.; Basak, A. J. *Am. Chem. Soc.* **1981**, *103*, 1604; (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935.

TABLE 1

[3+2] ANNULATIONS EMPLOYING ALLENYLSILANES

Allenophile	Allene	Annulation Product	% Yield
	$\text{H}_2\text{C}=\text{C}=\text{C}(\text{SiMe}_3)\text{Me}$		71-75
			86
			49
			91
			90
			71
		 13-19 : 1	68
	$\text{Me}_2\text{C}=\text{C}=\text{C}(\text{SiMe}_3)\text{Me}$		53
			63

**Chemical Abstracts Nomenclature (Collective Index Number):
(Registry Number)**

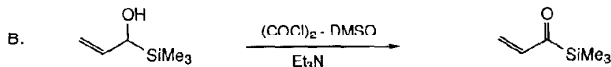
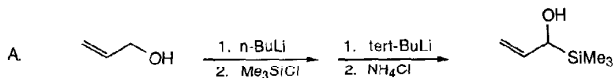
cis-4-exo-Isopropenyl-1,9-dimethyl-8-(trimethylsilyl)bicyclo[4.3.0]non-8-en-2-one: 4H-Inden-4-one, 1,3a,5,6,7,7a-hexahydro-3,3a-dimethyl-6-(1-methylethenyl)-2-(trimethylsilyl)-, (3a α ,6 α ,7a α)- (10); (77494-23-6)

(R)-(-)-Carvone: p-Mentha-6,8-dien-2-one, (R)-(-)- (8); 2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-, (R)- (9); (6485-40-1)

1 Methyl-1-(trimethylsilyl)allene: Silane, trimethyl(1-methyl-1,2-propadienyl)- (10); (74542-82-8)

(1-oxo-2-propenyl)trimethylsilane

(Silane, trimethyl(1-oxo-2-propenyl)-)



Submitted by Rick L. Danheiser, David M. Fink, Kazuo Okano, Yeun-Min Tsai,
and Steven W. Szczepanski.¹

Checked by Masahiko Hayashi and Ryoji Noyori.

1. Procedure

A. *(1-Hydroxy-2-propenyl)trimethylsilane*. A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two pressure-equalizing dropping funnels (250 and 500 mL), and a Claisen adapter fitted with an argon inlet adapter and a rubber septum (Note 1). The flask is charged with 20.0 g (0.344 mol) of allyl alcohol (Note 2), and 400 mL of dry tetrahydrofuran (Note 3), and then cooled below -75°C with a dry-ice acetone bath and maintained at that temperature while 157 mL (0.363 mol) of a 2.31 M solution of *n*-butyllithium in hexane (Note 4) is added dropwise over 1 hr. After 50 min, a solution of 39.3 g (0.362 mol) of chlorotrimethylsilane (Note 5) in 25 mL of tetrahydrofuran is added dropwise via syringe over 30 min, and the resulting colorless reaction mixture is stirred for 1 hr further, and then treated dropwise over 1.5 hr with 258 mL (0.415 mol) of a 1.61 M solution of

tert-butyllithium in pentane (Note 4). After 2 hr of further stirring at -75°C the cold bath is removed, and 100 mL of saturated ammonium chloride solution is added in one portion to the yellow reaction mixture. The resulting solution is stirred for 5 min, and then diluted with 50 mL of water and 300 mL of pentane. The organic phase is separated and washed successively with three 100-mL portions of water and two 100-mL portions of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated by carefully distilling off the solvents at atmospheric pressure through a 10-cm Vigreux column. The residual pale yellow liquid is transferred to a 100-mL round-bottomed flask, and the remaining volatile impurities are removed by distillation at 15 mm through a 4-cm column packed with glass helices (Note 6), leaving 35.1-39.7 g of (1-hydroxy-2-propenyl)trimethylsilane as a pale yellow liquid (Notes 7 and 8) used in the next step without further purification.

B. *(1-Oxo-2-propenyl)trimethylsilane*. A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer and two 250-mL pressure-equalizing dropping funnels, one of which is fitted with an argon inlet adapter (Note 1). The flask is charged with 41.71 g (0.329 mol) of oxalyl chloride (Note 9) and 500 mL of dichloromethane (Note 10), and cooled below -75°C with a dry ice-acetone bath and maintained at that temperature while a solution of 55.82 g (0.715 mol) of dimethyl sulfoxide (Note 11) in 60 mL of dichloromethane is added dropwise over 1 hr. After 1 hr, a solution of the crude (1-hydroxy-2-propenyl)trimethylsilane in 100 mL of dichloromethane is added dropwise over 1.25 hr to the colorless reaction mixture, which is stirred at -75°C for 1 hr further, and then treated dropwise over 30 min with 150.38 g (1.486 mol) of triethylamine (Note 12). After 1 hr, the cold bath is removed and the reaction mixture is poured into 200 mL of water. The organic

phase is separated and washed successively with five 100-mL portions of 10% hydrochloric acid, three 100-mL portions of water, and two 100-mL portions of saturated sodium chloride solution. dried over anhydrous sodium sulfate. filtered, and concentrated by carefully distilling off the solvents at atmospheric pressure through a 10-cm Vigreux column. The residual yellow oil is transferred to a 250-mL, round-bottomed flask containing 0.050 g of 3-tert-butyl-4-hydroxy-5-methylphenyl sulfide (Note 13) and distilled through a 4-cm column packed with glass helices to afford 27.8-30.0 g (63-68% overall yield based on allyl alcohol) of (1-oxo-2-propenyl)trimethylsilane as a brilliant yellow oil, bp 47-50°C (30 mm) (Notes 14 and 15).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven, and then assembled and maintained under an atmosphere of argon during the course of the reaction.

2. Allyl alcohol was purchased from Aldrich Chemical Company, Inc. and distilled from calcium hydride prior to use.

3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

4. n-Butyllithium was purchased from Aldrich Chemical Company, Inc. or Mitsuwa Pure Chemicals. tert-Butyllithium was obtained from Aldrich Chemical Company, Inc. These were titrated using the method of Watson and Eastham^{2a} (submitters) or Lipton^{2b} (checkers).

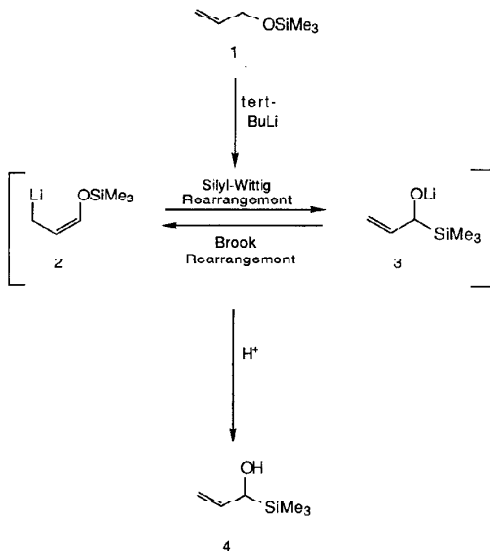
5. Chlorotrimethylsilane was obtained from Petrarch Systems, Inc., or Shin-etsu Kagaku Co., and distilled from calcium hydride before use.

6. The heating bath temperature was not permitted to exceed 70°C during the course of the distillation.
7. The purity of this material was determined to be 95% by gas chromatographic analysis (10% OV-101 on 100-120 mesh Chromosorb W, 6 ft x 1/8 in, program: 50°C for 2 min and then 50-250°C at 32°C/min).
8. The product exhibits the following spectral properties: IR (film) cm^{-1} : 3420, 2955, 2895, 2820, 1625, 1410, 1245, 1140, 1095, 990, 900, and 840; ^{13}C NMR (67.9 MHz, CDCl_3) δ : -4.4, 68.9, 109.4, 139.9; ^1H NMR (250 MHz, CDCl_3) δ : 0.05 (s, 9 H), 2.86 (br s, 1 H), 3.88 (m, 1 H), 4.86 (ddd, 1 H, J = 2, 2, 11), 4.98 (ddd, 1 H, J = 2, 2, 17), 5.89 (ddd, 1 H, J = 5.5, 11, 17); HRMS m/e calcd for $\text{C}_6\text{H}_{14}\text{OSi}$ (M^+): 130.0814, found: 130.0810.
9. Oxalyl chloride purchased from Aldrich Chemical Company, Inc. was fractionally distilled under argon before use.
10. Dichloromethane was distilled from calcium hydride immediately before use.
11. Dimethyl sulfoxide was distilled from calcium hydride immediately before use.
12. Triethylamine was distilled from calcium hydride before use.
13. 3-tert-Butyl-4-hydroxy-5-methylphenyl sulfide was purchased from Aldrich Chemical Company, Inc.
14. The purity of this material was determined to be >97% by gas chromatographic analysis (10% OV-101 on 100-120 mesh Chromosorb W, 6 ft x 1/8 in, program: 50°C for 2 min and then 50-250°C at 32°C/min).
15. The product exhibits the following spectral properties. IR (film) cm^{-1} : 2960, 2900, 1635, 1600, 1590, 1415, 1390, 1255, 1185, 985, 960, and 845; ^{13}C NMR (67.9 MHz, CDCl_3) δ : -2.2, 128.5, 141.3, 237.9; ^1H NMR (250 MHz, CDCl_3) δ : 0.23 (s, 9 H), 5.94 (dd, 1 H, J = 1, 11), 6.13 (dd, 1 H, J = 1, 18), 6.38 (dd, 1 H, J = 11, 18).

3. Discussion

(1-Oxo-2-propenyl)trimethylsilane has previously been prepared by Reich and co-workers in four steps beginning with propargyl alcohol.³ This earlier synthesis proceeded in 45% overall yield and involved as key steps the metalation (at -90°C) and silylation of 1-(1-ethoxyethoxy)-1,2-propadiene, followed by careful hydrolysis of the resulting α -silyl allenyl ether.

The present method⁴ offers a more efficient and convenient two-step route to the parent α,β -unsaturated acylsilane derivative. The first step in the procedure involves the conversion of allyl alcohol to allyl trimethylsilyl ether, followed by metalation⁵ (in the same flask) with tert-butyllithium at -75°C. Protonation of the resulting mixture of interconverting lithium derivatives (2 and 3) with aqueous ammonium chloride solution furnishes (1-hydroxy-2-propenyl)trimethylsilane (4), which is smoothly transformed to (1-oxo-2-propenyl)trimethylsilane by Swern oxidation.⁶ The acylsilane is obtained in 63-68% overall yield from allyl alcohol in this fashion.



α,β -Unsaturated acylsilanes serve as valuable building blocks for the synthesis of a variety of complex organic compounds. These α,β -unsaturated carbonyl derivatives participate in a number of carbon-carbon bond forming processes including organocuprate conjugate additions,³ TiCl_4 -mediated conjugate allylations,⁷ Diels-Alder reactions,³ 1,3-dipolar cycloadditions,⁸ and the [3+2] annulation method recently developed in our laboratory.⁸ The utility of these reactions is enhanced by the fact that the product acylsilanes are subject to a variety of useful further transformations,⁹ including, for example, Brook reactions,^{3,10} oxidation to carboxylic acids,¹¹ and fluoride-promoted conversion to ketones and aldehydes.^{11b,12} The present procedure provides a practical method for the preparation of multigram quantities of the simplest α,β -unsaturated acylsilane.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(1-Oxo-2-propenyl)trimethylsilane: Silane, trimethyl(1-oxo-2-propenyl)- (9); (51023-60-0)

(1-Hydroxy-2-propenyl)trimethylsilane: 2-Propen-1-ol, 1-(trimethylsilyl)- (11); (95061-68-0)

Allyl alcohol (8); 2-Propen-1-ol (9); (107-18-6)

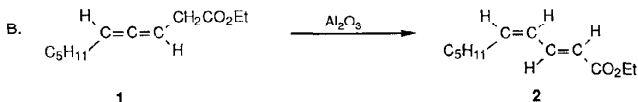
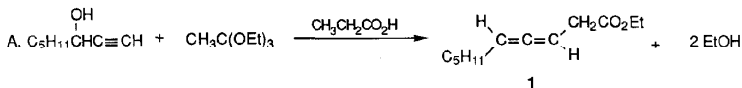
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)

3-tert-Butyl-4-hydroxy-5-methylphenyl sulfide: o-Cresol, 4,4'-thiobis[6-tert-butyl- (8); Phenyl, 4,4'-thiobis[2-(1,1-dimethylethyl)-6-methyl- (9); (96 66 2)

ETHYL (E,Z)-2,4-DECADIENOATE

(2,4-Decadienoic acid, ethyl ester, (E,Z)-)



Submitted by S. Tsuboi, T. Masuda, S. Mimura, and A. Takeda.¹

Checked by Mark A. Henderson and Clayton H. Heathcock.

Caution! See benzene warning, Org. Synth. 1978, 58, 168.

A. *Ethyl 3,4-decadienoate* (1).² A 300-mL, round-bottomed flask equipped with a reflux condenser is charged with 12.1 g (0.096 mol) of 1-octyn-3-ol (Note 1), 100 g (0.616 mol) of triethyl orthoacetate (Note 2), and 0.24 g (3.2 mmol) of propionic acid. The solution is heated at 140-150°C in an oil bath. Every 2 hr, the ethanol produced is removed under reduced pressure with a rotary evaporator, and then 10 g (0.062 mol) of triethyl orthoacetate and 0.024 g (0.32 mmol) of propionic acid are added. The mixture is heated until the starting material is consumed (6-8 hr) (Note 3). Excess triethyl orthoacetate is removed under reduced pressure (Note 4). The residue is distilled under reduced pressure to give 15.4-17.2 g (82-91%) of 1 (Note 5) as a clean oil, bp 80-85°C (0.3 mm).

B. *Ethyl (E,Z)-2,4-decadienoate* (2). A dry, 500-mL, round-bottomed flask is charged with 50 g of aluminum oxide (Note 6) and heated at 200°C for 2 hr under reduced pressure (0.05 mm). The flask is fitted with a reflux condenser connected to a nitrogen line and a heavy magnetic stirring bar is added (Note 7); the flask is flushed with nitrogen. With positive nitrogen pressure, the flask is charged with 200 mL of benzene (Note 8) and 15.4-17.2 g (78-88 mmol) of allenic ester 1. The mixture is heated at reflux temperature with vigorous stirring for 5 hr. The aluminum oxide is removed by filtration with suction through a sintered-glass funnel of medium porosity and thoroughly washed with 100 mL of ethyl acetate (Note 9). The combined filtrate is concentrated with a rotary evaporator to afford 11.6-13.6 g (75-88%) of nearly pure 2 as a clean oil (Notes 10 and 11), bp 83-88°C (0.1 mm).

2. Notes.

1. 1-Octyn-3-ol was used as supplied by Aldrich Chemical Company, Inc. (96% purity).

2. Triethyl orthoacetate was used as supplied by Aldrich Chemical Company, Inc. (97% purity) or by Tokyo Kasei Kogyo Co., Ltd. (98% purity).

3. The checkers removed the ethanol with a rotary evaporator and replaced it with fresh triethyl orthoacetate (10 g) and propionic acid (0.024 g) after 2, 4, and 6 hr.

4. The checkers removed excess triethyl orthoacetate under reduced pressure (0.05 mm) overnight. The recovered material may be easily purified by distillation and reused.

5. The product might contain trace amounts of triethyl orthoacetate, but it can be used for the next step since aluminum oxide adsorbs triethyl orthoacetate. The product² is characterized by IR (neat) cm^{-1} : 1970 and 1740; ^1H NMR (CCl_4) δ : 0.92 (t, 3 H, $\text{CH}_3(\text{CH}_2)_4$), 1.29 (t, 3 H, OCH_2CH_3), 1.32 (m, 6 H, $\text{CH}_3(\text{CH}_2)_3$), 1.91 (m, 2 H, $\text{CH}_2\text{CH=}$), 2.90 (m, 2 H, $\text{CH}_2\text{CO}_2\text{Et}$), 4.08 (q, 2 H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.09 (m, 2 H, CH=C=CH).

6. Weakly basic alumina³ (200-300 mesh) for column chromatography is used. The checkers used Alumina Woelm-B, Akt. 1.

7. Efficient stirring is essential to the success of this reaction.

8. Aprotic solvents such as xylene, chlorobenzene, and toluene can be used instead of benzene. If the boiling point of the product is close to that of the solvent, the mixture of aluminum oxide and the allene may be heated to distil at ca. 150°C under an atmosphere of nitrogen.

9. The checkers found that the use of more than 100 mL of ethyl acetate gives a less pure final product.

10. Gas chromatographic analysis (capillary column coated with thermon-1000, 30 m, 140°C) indicated that the product was ca. 93% pure. Impurities consisted of the 2E,4E isomer (5%) and an unidentified compound (2%).

11. The proton magnetic resonance spectrum is as follows (CCl_4) δ : 0.90 (t, 3 H, $J = 6$, $\text{CH}_3(\text{CH}_2)_4$), 1.28 (t, 3 H, $J = 7$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.40 (m, 6 H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2$), 1.9-2.6 (m, 2 H, $\text{CH}_2\text{CH=CH}$), 4.12 (q, 2 H, $J = 7$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.4-6.3 (m, 3 H, $\text{CH=CH-CH=CHCO}_2\text{Et}$), 7.46 (dd, 1 H, $J = 10$ and 15 , $\text{CH=CHCO}_2\text{Et}$); n_D^{25} 1.4895.

Ethyl (E,Z)-2,4-decadienoate has been prepared in several ways: (a) the addition of lithium di-(Z)-1-heptenylcuprate to ethyl propiolate⁴ (90% yield, 95% purity; 27-32% overall yield based on (Z)-1-bromoheptene),⁵ (b) the reaction of 1-heptenylmagnesium bromide with ethyl (E)- β -(N,N-diethylamino)acrylate (32% yield, 89% purity),⁶ (c) the Wittig reaction of hexyltriphenylphosphonium bromide with ethyl (E)-4-oxo-2-butenolate (68% yield, 85% purity).⁷ These known methods involving the use of organometallic reagents need anhydrous conditions at low temperatures (-8° to -40°C). The separation of triphenylphosphine oxide from the reaction mixture in a Wittig reaction is occasionally not easy.

The present procedure offers an experimentally simple and less expensive preparation of ethyl (E,Z)-2,4-decadienoate under essentially neutral conditions. It allows large scale preparation since the starting materials are not sensitive to air or moisture. In addition, the reaction proceeds stereoselectively, and the yields of product are generally high. Several examples are listed in Table 1 to show the scope of the method.

There are many compounds containing a conjugated (E,Z)-diene structure in naturally occurring compounds such as flavors,^{3,8} insect pheromones,^{3,9} and leukotrienes.¹⁰ The present procedure has been used for the syntheses of bombykol,³ megatomoic acid,¹¹ (\pm)-leukotriene A₄ methyl ester,¹² and (E,Z)-2,4-dienamides.¹³

TABLE I

Rearrangement of β -Allenic Esters to (E,Z)-2,4-Dienoic Esters with Alumina²

Starting Material	Product	Yield (%) ^a	Purity (%) ^b
		57	90
		82	96
		80	96
		69	93
		67	93
		82	99
		87	91
		70	96

^aIsolated yield^bPurity determined by gas chromatography

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl (E,Z)-2,4 decadienoate: 2,4-Decadienoic acid, ethyl ester,
(E,Z)- (8,9); (3025-30-7)

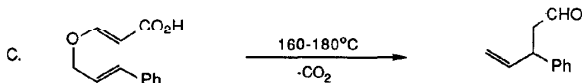
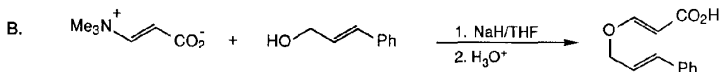
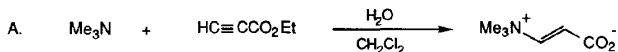
Ethyl 3,4-Decadienoate: 3,4-Decadienoic acid, ethyl ester (9); (36186-28-4)
1-Octyn-3-ol (8,9); (818 72-4)

Triethyl orthoacetate: Orthoacetic acid, triethyl ester (8); Ethane, 1,1,1-triethoxy- (9); (78-39-7)

α -UNSUBSTITUTED γ,δ -UNSATURATED ALDEHYDES BY CLAISEN

REARRANGEMENT: 3-PHENYL-4-PENTENAL

(Benzenepropanal, β -ethenyl-)



Submitted by Dennis E. Vogel and George H. Büchi.¹

Checked by Tadahito Nobori and Ryoji Noyori.

1. Procedure

A. (*E*)-(Carboxyvinyl)trimethylammonium betaine. A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, dropping funnel, and thermometer. The flask is charged with 25.0 g (0.255 mol) of ethyl propiolate (Note 1), 14 mL of dichloromethane and 440 mL of water. The mixture is cooled to 5°C (Note 2) and 90 mL (0.35 mol) of an aqueous 25% solution of trimethylamine (Note 3) is added under vigorous stirring over a period of 30 min. The reaction temperature remains between 0 and 5°C during the addition and then is allowed to warm to 25°C for 3 hr. The

dichloromethane layer is separated and the aqueous layer is washed three times with 100-mL portions of dichloromethane. The aqueous layer is placed in a 1-L, round-bottomed flask and concentrated at 15 mm pressure with a rotary evaporator equipped with a dry ice condenser. The flask is heated to approximately 45°C. When the residue gives the appearance of a wet solid, it is treated with 150 mL of dioxane and concentrated as described above. Dioxane treatment followed by concentration is repeated three more times with 150-mL portions of dioxane (Note 4). The yellow solid residue is triturated with acetonitrile (Note 5) until a white solid is obtained. The solid is collected and dried at 0.1 mm, 25°C for 14 hr to give 25.0-26.9 g (76-82% yield) of (E)-(carboxyvinyl)trimethylammonium betaine, mp 176-177°C (dec) (Note 6).

B. (E)-3-[(E)-3-Phenyl-2-propenoxy]acrylic acid. An oven dried, 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel and reflux condenser is purged with argon and charged with 8.20 g (0.171 mol) of 50% sodium hydride in oil (Note 7) and 90 mL of anhydrous tetrahydrofuran (Note 8). To this mixture is added a solution of 19.0 g (0.143 mol) of cinnamyl alcohol (Note 9) in 180 mL of anhydrous tetrahydrofuran. The mixture is stirred for 30 min at which point 25.0 g (0.194 mol) of (E)-(carboxyvinyl)trimethylammonium betaine is added and the reaction mixture is heated at a gentle reflux for 15 hr. The cooled reaction mixture is slowly added to a mixture of 600 mL of water and 220 mL of a saturated aqueous solution of sodium chloride (Note 10). The residual material is removed with wet ether (Note 11) and added to the aqueous solution. The aqueous layer is washed three times with 450 mL of ether and acidified with approximately 21 mL of concentrated hydrochloric acid to pH 1. This mixture is extracted three times with 700 mL of ether and the ether

layer is dried with 20 g of anhydrous magnesium sulfate for 30 min. The mixture is filtered and the filtrate is concentrated, first with a rotary evaporator and then at 0.1 mm for 24 hr at 25°C to give crude (E)-3-[(E)-3-phenyl-2-propenoxy]acrylic acid. This material can be used in Part C without further purification. However, purification by trituration with approximately 30 mL of anhydrous ether gives 24.7-25.0 g (85% yield) of white crystalline product, mp 140-141.5°C (dec) (Note 12).

C. 3-Phenyl-4-pentenal. In a 100-mL, round-bottomed flask equipped with a magnetic stirring bar is placed 20.1 g (0.098 mol) of (E)-3-[(E)-3-phenyl-2-propenoxy]acrylic acid from B (Note 13). The flask is fitted with a distillation head for vacuum distillation and heated at 0.1 mm pressure. The oil bath temperature is maintained between 160-165°C while the mixture is stirred, until all the material melts. Once the initial reaction is under control the oil bath is slowly heated to 180°C. The product is collected in a receiver flask cooled with a dry ice-acetone bath to give 13.3-14.3 g (84-91% yield) of 3-phenyl-4-pentenal, bp 114-115°C (15 mm) (Note 14).

2. Notes

1. Ethyl propiolate, purchased from Aldrich Chemical Company, Inc., is freshly distilled prior to use.
2. An ice-acetone bath is used to cool the reaction mixture.
3. An aqueous 25% solution of trimethylamine available from Aldrich Chemical Company, Inc. is used directly.
4. This procedure helps to concentrate further the product by forming an azeotrope with the water.

5. Continued trituration with small portions of acetonitrile (e.g., eight times with 50-mL portions) eventually removes all traces of the yellow-colored impurity as well as any residual water.

6. The product exhibits the following spectral properties: IR (KBr) cm^{-1} : 1665, 1600, 1360; ^1H NMR (D_2O , DSS ref) δ : 3.3 (br s, 9 H, $(\text{CH}_3)_3\text{N}$), 6.3 (br d, 1 H, $J = 13$, vinyl CH), 6.8 (br d, 1 H, $J = 13$, vinyl CH).

7. A suspension of 50% sodium hydride in mineral oil, purchased from Alfa Products, Morton/Thiokol Inc. or Nakarai Chemicals, Ltd., is used directly.

8. Anhydrous tetrahydrofuran is obtained by distillation from benzophenone ketyl prior to use.

9. Cinnamyl alcohol purchased from Aldrich Chemical Company, Inc. is freshly distilled before use. The checkers purchased it from Nakarai Chemicals, Ltd.

10. *Caution.* Residual sodium hydride is present in the reaction mixture; however, it can be quenched safely by strict adherence to the procedure described.

11. The use of wet ether has two purposes. Not only does the ether help wash residue product from the flask, but ether which has not been carefully dried contains traces of water which allows for the safe quenching of the last traces of sodium hydride.

12. The product exhibits the following spectral properties: IR (KBr) cm^{-1} : 1680, 1615, 1600; ^1H NMR (CDCl_3 60 MHz) δ : 4.5 (d, 2 H, $J = 5.5$, $\text{OCH}_2\text{CH=}$), 5.2 (d, 1 H, $J = 12$, $\text{CH=CHCO}_2\text{H}$), 6.5 (m, 2 H, PhCH=CH-), 7.2 (s, 5 H, Ph-), 7.5 (d, 1 H, $J = 12$, $\text{O-CH=CHCO}_2\text{H}$), 12.0 (s, 1 H, CO_2H).

13. The material obtained from trituration of the crude product in Part B can also be used at this point and gives similar results.

14. The product exhibits the following spectral properties: IR (neat) cm^{-1} : 2840, 2740, 1720, 1640, 1600; ^1H NMR (CDCl_3 , 60 MHz) δ : 2.9 (d, d 2 H, $J = 2, 4$, $\text{CH}_2\text{-CHO}$), 4.0 (q, 1 H, $J = 7$, Ph-CH), 5.0 (d, 1 H, $J = 7$, vinyl), 5.3 (s, 1 H, vinyl), 6.0 (m, 1 H, vinyl), 7.2 (s, 5 H, Ph), 9.5 (t, 1 H, $J = 2$, CHO).

3. Discussion

The procedure described² illustrates a new general synthetic method for the preparation of (E)-3-allyloxyacrylic acids and their conversion to α -unsubstituted γ,δ -unsaturated aldehydes by subsequent Claisen rearrangement-decarboxylation. Such aldehydes are traditionally prepared by Claisen rearrangements of allyl vinyl ethers.³ Allyl vinyl ethers are typically prepared by either mercury-catalyzed vinyl ether exchange with allylic alcohols or acid-catalyzed vinylation of allylic alcohols with acetals. The basic conditions required for alkoxide addition to the betaine to produce carboxyvinyl allyl ethers, as described in this report, nicely complements these two methods. In addition, this Claisen rearrangement is an experimentally very simple procedure, since sealed tube and other high pressure vessels are not required. The allyloxyacrylic acids are heated neat (in most cases a small amount of hydroquinone is added) and, by adjusting the pressure at which the reaction is performed, the aldehyde products distill from the reaction mixture in analytically pure form.

(E)-(Carboxyvinyl)trimethylammonium betaine is prepared by a modification of the procedure of McCulloch and McInnes.⁴ They also reported the addition of simple alkoxides to this betaine, and that deuterium exchange is not observed when this reaction is performed with the deuterated betaine. We have also observed that replacement of the betaine with propionic acid leads to the

formation of 3-alkoxyacrylic acids in significantly lower yields.² These observations are best accounted for by an addition-elimination process.

This procedure provides a variety of allyloxyacrylic acids; however, it is sensitive to steric hindrance. Tertiary allylic alcohols do not add to the betaine and sterically hindered secondary alcohols add with decreasing facility. Table I indicates the scope of this reaction.

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TABLE I
PREPARATION AND REARRANGEMENT OF 3-ALLYLOXYACRYLIC ACIDS

Starting Material	Yield of Adduct, %	Product	Yield, %
	89		68
	84		78
	92		quant.
	62		quant.
	90		quant.
	53, 77		quant.
	82		79
			16
	55		82

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Phenyl-4-pentenal: Benzenepropanal, β -ethenyl- (9); (939-21-9)

(E)-(Carboxyvinyl)trimethylammonium betaine: Ethenaminium, 2-carboxy-N,N,N-trimethyl-, hydroxide, inner salt, (E)- (9); (54299-83-1)

Ethyl propiolate: Propiolic acid, ethyl ester (8); 2-Propynoic acid, ethyl ester (9); (623-47-2)

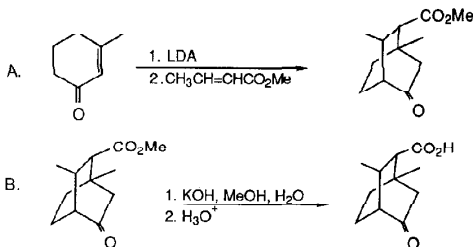
(E)-3-[(E)-3-Phenyl-2-propenoxy]acrylic acid: 2-Propenoic acid, 3-[(3-phenyl-2-propenyl)oxy]-, (E,E)- (10); (88083-18-5)

Cinnamyl alcohol (8); 2-Propen-1-ol, 3-phenyl- (9); (104-54-1)

APROTIC DOUBLE MICHAEL ADDITION:

PREPARATION OF 1,3-DIMETHYL-5-OXOBICYCLO[2.2.2]OCTANE-2-CARBOXYLIC ACID

(Bicyclo[2.2.2]octane-2-carboxylic acid, 1,3-Dimethyl-5-oxo-)



Submitted by Dietrich Spitzner and Anita Engler.¹

Checked by Michael P. Trova, Mary A. Kinsella, and Leo A. Paquette.

1. Procedure

A. *Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate.*² An oven-dried, 250-mL, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with 100 mL of dry tetrahydrofuran and 5.56 g (55 mmol) of anhydrous diisopropylamine. The flask is flushed with argon via a needle inlet-outlet and cooled to -78°C with a dry ice-isopropyl alcohol bath (Notes 1-3). To the stirred solution is added dropwise with a syringe 30 mL (54 mmol) of a 1.8 M solution of butyllithium in hexane (Note 4) to form lithium diisopropylamide, followed after 30 min by a solution of 5.50 g (50 mmol) of 3-methyl-2-cyclohexen-1-one (Note 5) in 60 mL of dry tetrahydrofuran via a flex-needle over a period of 15 min. Stirring and cooling is continued for an additional 30 min. To the resulting yellow solution of the lithium

dienolate, 10.0 g (0.1 mol) of methyl (E)-crotonate (Note 6) is added with a syringe within 2 min. The cooling bath is removed and the reaction mixture is allowed to warm to room temperature (Note 7). Stirring is continued at room temperature for 2 hr. The reaction mixture is quenched by adding 1 N hydrochloric acid until the mixture turns acidic. Extraction with three 80-mL portions of dichloromethane followed by evaporation of the solvent yields a light yellow oil which is taken up in 100 mL of diethyl ether. This solution is filtered through 100 g of silica gel to remove polymers and water. Elution with diethyl ether and evaporation of the solvent gives a yellow oil which is distilled in a Kugelrohr distillation apparatus (Note 8) under reduced pressure. After a small forerun (ca. 0.5 g of unreacted 3-methyl-2-cyclohexen-1-one) at 50°C, 0.05 mm, the main fraction is collected at 110-120°C (oven temperature), 0.05 mm to give 8.25-9.43 g (78-90%) of a colorless oil, which solidifies on standing in the freezer. One recrystallization from cold pentane (approximately 10 mL of pentane per 8 g of ester mixture) gives 6.0 g of product as white crystals, mp 37°C (Note 9), of approximately 97% isomeric purity (Note 10).

B. *1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid*. A mixture of 11.2 g (53.4 mmol) of the foregoing crude ester in 40 mL of methanol and 8.0 g (143 mmol) of potassium hydroxide in 16 mL of water is refluxed under argon until the ester is no longer present when monitored by TLC (Note 7). This takes about 1 day. Methanol is distilled off with a rotary evaporator, and the remaining dark solution is extracted with ether (2 x 50 mL), acidified to pH 1 with dilute sulfuric acid and extracted with dichloromethane (4 x 50 mL). The organic layer is filtered through 100 g of silica gel and eluted with ether to remove most of the dark impurities. Concentration under reduced pressure gives 10.0 g of acid mixture. Distillation in a Kugelrohr apparatus

at 180°C, 0.03 mm and one recrystallization from ether-pentane gives 7.0 g (67%) of pure bicyclic acid (isomeric purity greater than 98%) as white crystals, mp 130-131°C (Note 11).

2. Notes

1. All glassware, syringes and flex-needles were baked in an oven at 120°C overnight and assembled while hot.

2. Tetrahydrofuran was purified by passing it through activated (12 hr at 450°C) neutral aluminum oxide purchased from ICN and distilling it fresh from lithium aluminum hydride.

3. Diisopropylamine was distilled from calcium hydride prior to use.

4. Butyllithium in hexane was purchased from Metallgesellschaft AG, Frankfurt, Germany and standardized by titration with diphenylacetic acid.³

5. 3-Methyl-2-cyclohexen-1-one was purchased from Aldrich-Europe, but is easily prepared from ethyl acetoacetate and paraformaldehyde.⁴

6. Methyl crotonate may polymerize to some extent under these conditions. An excess is used in order to insure complete formation of the product. Unreacted methyl crotonate is easily removed by distillation.

7. The reaction was monitored by TLC (silica gel 60PF254, Merck, Darmstadt, Germany; 1:1 diethyl ether:pentane as the mobile phase, 2,4-dinitrophenylhydrazine as revealing reagent) and by GLC (N₂, 3% SE30 rubber on Volaspher A2, Merck, Darmstadt, Germany, 140°C isotherm). The Michael reaction is very slow at -78°C. and the optimum temperature depends upon the acceptor (Table I).

8. A Büchi rotary evaporator was used.

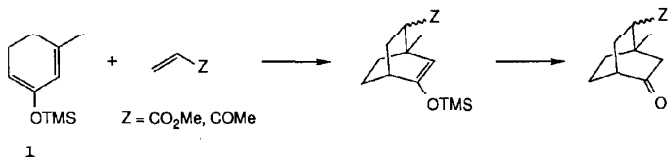
9. The spectra are as follows: IR (neat) cm^{-1} : 1730 (ester, ketone); EI-GCMS (70 eV): m/e = 210 (M^+ , 5%), 110 (100), 95 (30); $^1\text{H-NMR}$ (250 MHz, CDCl_3 , TMS) δ : 0.94 (s, Me, 3 H), 1.10 (d, 3 H, J = 7), 1.30-2.35 (m, 8 H), 2.75 (dd, 1 H, J = 3 and 19), 3.67 (s, OMe).

10. The oily product contains approximately 8% of the exo isomer (estimated by $^1\text{H-NMR}$ on the basis of the ester methyl at 3.70 ppm (major) and at 3.67 ppm (minor)).

11. An additional 1.2 g (9.5%) of pure acid may be recovered from the mother liquor. The spectra are as follows: $^{13}\text{C-NMR}$ (62.88 MHz, CDCl_3) δ : 17.3 (t), 17.4 (q), 23.7 (q), 31.8 (d), 33.9 (t), 35.7 (s), 44.9 (t), 47.9 (d), 50.9 (q), 54.5 (d), 174.8 (s), 214.1 (s); $^1\text{H-NMR}$ (250 MHz, CDCl_3) δ : 1.05 (s, 3 H), 1.15 (d, 3 H, J = 6.8), 1.35-2.15 (m, 8 H), 2.32 (m, 1 H), 2.81 (dd, 1 H, J = 19, 3), 11.2 (broad s, 1 H); EI-MS (70 eV): m/z = 196 (M^+ , 40%), 178 (5), 110 (100), 95(45); IR (CH_2Cl_2) cm^{-1} : 3480(m), 2920(s), 1725(s), 1705(s).

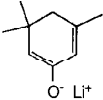
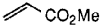
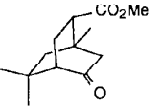

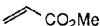
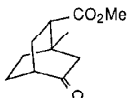

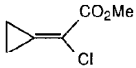
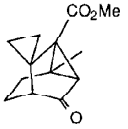

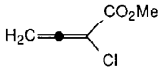
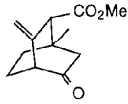
3. Discussion

The aprotic double Michael addition was discovered by R. A. Lee⁵ and used⁶⁻¹⁰ to synthesize functionalized bicyclo[2.2.2]octanes which may serve as starting materials in natural products syntheses (Table I). These bicyclo[2.2.2]octanes can also be obtained by a Diels-Alder cycloaddition of 2-trimethylsiloxy-substituted cyclohexadienes and dienophiles:¹¹



But there are many cases known where the (4+2) cycloaddition fails even with siloxy-activated dienes, e.g., methyl (E)-crotonate does not react with diene **1** at normal pressure and elevated temperature (110°C), whereas the aprotic double Michael addition does give the desired bicyclo[2.2.2]octane in high yield. This reaction gives mainly (92%) bicyclic esters with the endo configuration.

TABLE I
EXAMPLES OF CARBOCYCLIC ESTERS PREPARED BY THE APROTIC
DOUBLE MICHAEL ADDITION

Dienolate	Acceptor	Product	Yield(%)	Lit.
			98	4
			90	5
			64	8
			75	9

1. Institut für Chemie, University Hohenheim, Garbenstr. 30, D-7000 Stuttgart 70, Germany.
2. Hayiware, H.; Uda, H.; Kodama, T. *J. Chem. Soc., Perkin Trans. I* **1980**, 963.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

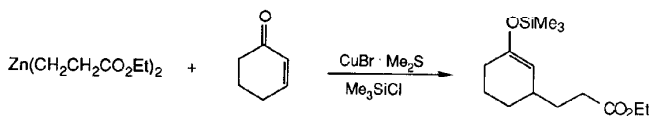
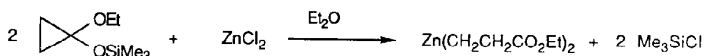
(Registry Number)

3-Methyl-2 cyclohexen-1-one: 2-Cyclohexen-1-one, 3-methyl- (8,9); (1193-18-6)
 (E)-Methyl crotonate: Crotonic acid, methyl ester, (E)- (8); 2-Butenoic acid, methyl ester, (E)- (9); (623-43-8)

COPPER-CATALYZED CONJUGATE ADDITION OF A ZINC HOMOEENOLATE:

ETHYL 3-[3-(TRIMETHYLSILOXY)CYCLOHEX-2-ENYL]PROPIONATE

(2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-, ethyl ester)



Submitted by Eiichi Nakamura and Isao Kuwajima.¹

Checked by Tina M. Kravetz, Daniel Cheney, and Leo A. Paquette.

1. Procedure

In a tared 1-L, three-necked flask, two necks of which are covered with rubber septa, and the other connected to a nitrogen/vacuum source, is placed 17.2 g of zinc chloride (Note 1). The flask is evacuated to approximately 2 mm and heated with a burner with swirling until practically all of the salt melts. The flask is cooled and filled with nitrogen. The dried salt weighs 16.4-17 g (ca. 0.12 mol) (Note 2). An efficient magnetic stirring bar and a Dimroth condenser in place of a rubber septum are set in position, and the flask is again flushed with nitrogen. Ether (300 mL) (Note 3) is introduced via the septum, and stirring is initiated and maintained throughout the reaction. The mixture is refluxed gently for 1 hr to aid dissolution of the

solid salt (Note 4). The flask is cooled, and 1-trimethylsilyloxy-1-ethoxycyclopropane (41.80 g, 0.24 mol) (Note 5) is introduced with the aid of a hypodermic syringe during 5 min. The cloudy mixture is stirred at room temperature for 1 hr; the more dense lower layer may mostly have disappeared at this point. The mixture is refluxed for 30 min to complete homoenolate formation. The clear, colorless solution of the zinc homoenolate and chlorotrimethylsilane is cooled in an ice bath, and cuprous bromide/dimethyl sulfide complex (0.4 g, 2 mmol) (Note 6) is added by removing the septum while nitrogen adequate to exclude air is introduced through the inlet. 2-Cyclohexen-1-one (9.62 g, 0.1 mmol) (Note 7) is introduced via the septum during 1 min, and then hexamethylphosphoric triamide (HMPA) (34.8 mL, 0.2 mol) (Notes 8,9) is added during 5 min. A slightly exothermic reaction occurs initially and the bath is removed after 20 min. After 3 hr at room temperature, 40 g of silica gel (Note 10) and 300 mL of dry hexane (Note 11) are added while the mixture is stirred vigorously for 3 min. The supernatant liquid is decanted, and the residue is suspended in 60 mL of dry ether. Dry hexane (60 mL) is added and the supernatant liquid is decanted. This extractive procedure is repeated once and the combined organic phase is filtered through Celite (Note 12). After concentration with a rotary evaporator, the oily product is distilled under reduced pressure (ca. 2 mm). 1-Trimethylsilyloxy-1-ethoxycyclopropane (8-10 g) is recovered as the first fraction (bp 26°C/2.3 mm). The majority of the HMPA remaining after workup distills at 80-120°C/2.3 mm. Finally, the desired product (18.9-20.5 g, 70-76%) is obtained as a fraction boiling at 130-132°C/2.3 mm (Note 13).

2. Notes

1. Zinc chloride was purchased from Koso Chemical Company and used as such (cf., *Org. Synth.* 1974, 54, 49). Alfa's ultra pure grade reagent resisted complete dissolution and appeared less suitable. The checkers used "Baker Analyzed" reagent zinc chloride with prior drying at 0.3 mm.

2. The amount of zinc chloride may be in slight excess of the theoretical amount (i.e., 0.5 equiv of the cyclopropane).

3. Ether was distilled from sodium benzophenone ketyl immediately before use.

4. A two-layer mixture results.

5. This cyclopropane was prepared according to an *Organic Syntheses* procedure, *Org. Synth.* 1985, 63, 147.

6. Cuprous bromide/dimethyl sulfoxide complex was purchased from Aldrich Chemical Company, Inc. and used as such.

7. Cyclohexenone was purchased from Tokyo Kasei Chemical Company or Aldrich Chemical Company, Inc. and used after simple distillation at reduced pressure.

8. Hexamethylphosphoric triamide (HMPA) was purchased from Tokyo Kasei Chemical Company and used after distillation from calcium hydride under reduced pressure.

9. This step was also checked substituting N,N'-dimethylpropyleneurea (DMPU),² supplied by Aldrich Chemical Company, Inc. or Fluka, for HMPA. The yield of final product dropped somewhat to 16.36-17.36 g (60-64%), but otherwise the reaction proceeded as described.

10. Ordinary silica gel (Wakogel C-300, Wako Chemical Company) was used.

11. Hexane was distilled from calcium hydride and stored over a potassium mirror. The checkers stored the redistilled hexane over molecular sieves.

12. Since the product has only moderate hydrolytic stability, the extractive procedure should be carried out rapidly under a flow of nitrogen. Operation in a nitrogen-filled plastic bag may eliminate the possibility of hydrolysis.

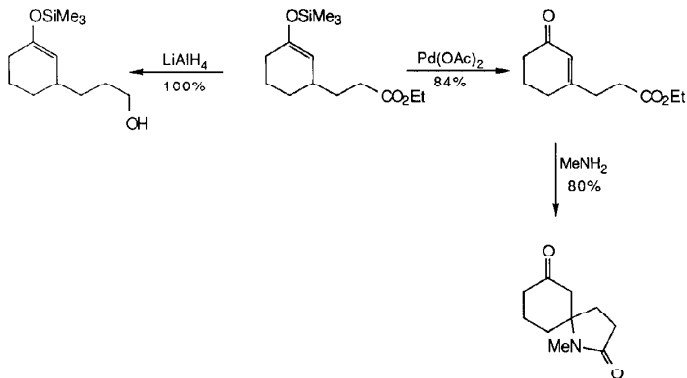
13. When the workup is performed as described (Note 11), the product may contain small amounts of residual HMPA and up to 5% (GLC estimation) of the keto ester resulting from hydrolysis of the enol silyl ether. Rf values of the keto ester and the silyl ether on thin layer analysis (Merck silica gel plates coated with a 0.25-mm layer of Kieselgel 60 F₂₅₄, developed with 30% ethyl acetate in hexane) were 0.4 and 0.8, respectively; gas chromatographic (GLC) analysis (OV-101, capillary glass column of 0.25-mm x 20-m, 120°C) showed retention times of 2.56 and 4.96 min for these two compounds, respectively. GLC analysis also indicated the ratio of the regioisomers of the enol silyl ether as >99:1 (4.96 and 6.13 min, respectively). On a smaller scale where the product can readily be handled on silica gel chromatography, a yield over 85% may be attained. Correct elemental analysis has been obtained for a sample purified by chromatography and distillation. Spectral properties of the product are as follows: ¹H NMR (300 MHz, CCl₄) δ: 0.04 (s, 9 H), 1.10 (t, 3 H, J = 7.1), 1.3-2.2 (m, 11 H), 3.93 (q, 2 H, J = 7.1), 4.55 (br s, 1 H); IR (neat film) cm⁻¹ 1730 (s), 1655 (s), 1445 (m), 1365 (s), 1245 (s), 1180 (vs), 840 (vs), 745 (s).

3. Discussion

Unlike their enolate counterparts, homoenolates have been underrated because of a prior lack of synthetic accessibility.³ Many of the previously known homoenolates cyclize readily to the cyclopropanolate tautomer and behave chemically as the latter. 1-Alkoxy-1-silyloxycyclopropanes⁴ have provided,

for the first time, examples of reactive yet characterizable homoenolates (of alkyl propionates). A titanium homoenolate undergoes 1,2-addition to carbonyl compounds, providing an efficient synthetic route to γ -lactones.⁴ The present procedure represents an unique and highly efficient method for the preparation of the zinc homoenolate of an alkyl propionate and illustrates its copper-catalyzed conjugate addition.⁵ The reaction consists of two stages; the first part of the present procedure generates a mixture of the zinc homoenolate and chlorotrimethylsilane, from which the homoenolate can be isolated by removal of the volatile material under reduced pressure, and the second part involves the chlorotrimethylsilane-assisted conjugate addition of the transient copper homoenolate. Only one of the propionate moieties on the zinc metal is available for the conjugate addition. The reaction mechanism has already been discussed briefly.⁶

The reaction is applicable to a variety of enones, enals, and acetylenic carbonyl compounds (Table). No 1,2-addition is seen under copper-catalyzed conditions since the zinc homoenolate does not generally undergo a 1,2-addition reaction to carbonyl compounds. The conjugate adduct is useful for organic synthesis as indicated by the scheme on the next page. The enol silyl ether moiety acts either to protect or activate the ketone functionality. The ready hydrolytic generation of the keto ester from the conjugate adduct provides an efficient entry to 6-keto esters. Replacement of the enone with an acyl halide leads to 4-keto esters in high yield,⁵ and the palladium catalyzed reaction with aryl and vinyl halides gives 3-aryl- and 3-vinyl propionates.⁸ The purified homoenolate undergoes 1,2-addition to aldehydes in the presence of chlorotrimethylsilane.⁹


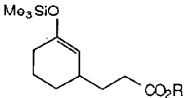

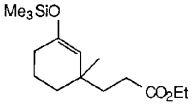

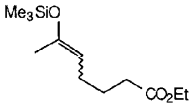
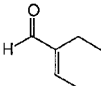
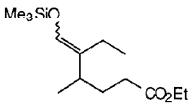

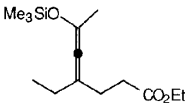

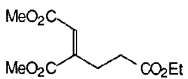


No other synthetic method is known that achieves the equivalent transformation. Rather elaborate procedures using an allylic anion type of the homoenolate "equivalents"⁶ or homoenolate radicals⁷ have been reported, but their tolerance to the structure of the enone acceptor is much narrower.

1. Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan.
2. Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
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9. Oshino, H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, 50, 2802.

TABLE
CONJUGATE ADDITION OF HOMOENOLATE OF ESTERS

Acceptor	Product	%Yield
		R = i-Pr 93 R = Et 76 R = Me 91
		92
		80
		75
		73
		63

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 3-[3-(trimethylsilyloxy)cyclohex-2-enyl]propionate. 2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-, ethyl ester (11); (90147-64-1)

Zinc chloride (8,9); (7646-85-7)

1-Trimethylsilyloxy-1-ethoxycyclopropane:

Silane, [(1-ethoxycyclopropyl)oxy]trimethyl- (8,9); (27374-25-0)

Cuprous bromide/dimethyl sulfide: Copper, bromo[thiobis[methane]]- (9); (54678-23-8)

Cyclohexenone: 2-Cyclohexen-1-one (8,9); (930-68-7)

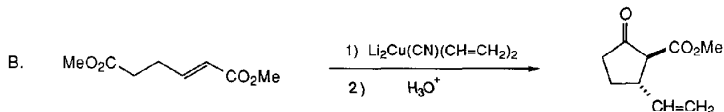
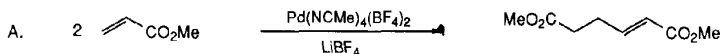
Hexamethylphosphoric triamide: Phosphoric triamide, hexamethyl- (8,9); (680-31-9)

N,N'-Dimethylpropyleneurea: 2(1H)-Pyrimidone, tetrahydro-1,3-dimethyl- (8,9); (7226-23-5)

CONJUGATE ADDITION/CYCLIZATION OF A CYANOCUPRATE:

2-CARBOMETHOXY-3-VINYLCYCLOPENTANONE

(Cyclopentanecarboxylic acid, 2-ethenyl-5-oxo-, methyl ester)



Submitted by William A. Nugent and Frank W. Hobbs, Jr.¹

Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. *Dimethyl (E)-2-hexenedioate*.² A 100-mL, one-necked, round-bottomed flask is capped by a septum, swept with dry nitrogen and flame-dried. The flask is charged with methyl acrylate (50 mL, 0.55 mol, Note 1), then anhydrous lithium tetrafluoroborate (9 g, 0.096 mol, Note 2), and finally tetrakis(acetonitrile)palladium tetrafluoroborate (1.33 g, 0.003 mmol, Note 3). The mixture is stirred briefly until homogeneous. It is warmed under nitrogen in a 40°C-oil bath for 72 hr (Note 4) and then allowed to cool to room temperature. The mixture is added to saturated aqueous sodium bicarbonate (100 mL) and extracted with ether (3 x 50 mL). The combined ether extracts are dried over anhydrous magnesium sulfate, filtered and concentrated to an oil with a rotary evaporator. The residue is distilled through a 10-cm

Vigreux column to give dimethyl (E)-2-hexenedioate (38.6 g, 81%, Note 5) as a colorless liquid, bp 100°C (1.1 mm).

B. *2-Carbomethoxy-3-vinylcyclopentanone*. A 1-L, three-necked, round-bottomed flask is fitted with a 125-mL pressure-equalizing addition funnel capped with a septum, an overhead stirrer and a septum. The apparatus is flame-dried and purged with dry nitrogen. The flask is charged through the addition funnel with tetravinyltin (12.48 g, 0.055 mol, Note 6) and anhydrous ether (250 mL). The solution is cooled to 0°C under nitrogen, and low-halide methyl lithium in ether (133 mL, 1.5 M, 0.20 mol, Note 7) is slowly added directly by syringe to the stirred solution. After 15 min, the vinyl lithium mixture is cooled in a dry ice-acetone bath to -78°C for 20 min. The septum on one neck is briefly removed, and copper(I) cyanide (9.31 g 0.107 mol, Note 8) is added all at once. The septum is replaced by a low-temperature thermometer in an adapter. The bath and reaction are allowed to warm under nitrogen slowly, with stirring, so that the internal temperature is -30°C after 1 hr (Note 9). The addition funnel is charged with dimethyl (E)-2-hexenedioate (6.89 g, 0.040 mol) and anhydrous ether (16 mL). The contents of the addition funnel are added dropwise over 30 min to the cuprate at -30°C, and stirring is continued under the nitrogen atmosphere for an additional 30 min at that temperature. A mixture of saturated aqueous ammonium chloride (80 mL) and water (80 mL) is added dropwise over 20 min through the addition funnel while the temperature of the system is allowed to rise. After the mixture is stirred for an additional 90 min it is filtered through a medium-porosity glass frit. The flask and filter cake are rinsed with water (2 x 30 mL) and ether (2 x 30 mL). The ether layer is separated and the aqueous layer is further extracted with ether (2 x 75 mL). The combined organic layers are washed with water (25 mL), dried over anhydrous magnesium sulfate and

concentrated with a rotary evaporator (Note 10). The residue (Note 11) is distilled through a short-path distillation apparatus to afford 2-carbomethoxy-3-vinylcyclopentanone (5.39 g, 80%, Note 12) as a colorless liquid, bp 65-70°C at 0.4 mm (Note 13).

2. Notes

1. Reagent grade methyl acrylate from Fisher Scientific Company, containing p-methoxyphenol as inhibitor, was used as received.

2. Anhydrous 98% pure lithium tetrafluoroborate (LiBF_4) from Alfa Products, Morton/Thiokol, Inc. was used as received.

3. The palladium complex was purchased from Strem Chemical Company and was used as received. Alternatively, material prepared from palladium sponge and nitrosonium tetrafluoroborate in acetonitrile³ worked equally well.

4. The greyish precipitate which begins to appear after ca. 40 hr is the 1:1 adduct of the product with lithium tetrafluoroborate.

5. Submitters find that the product typically contains 95% of 2-hexenedioates as measured by capillary column GLC (30 m DB17 column, 120°C isothermal). Retention times for the isomeric hexenedioates were (Z)-2 (2.44 min), (Z)-3 (2.75 min), (E)-3 (3.08 min), (E)-2 (3.44 min). TLC (30:70 ethyl acetate/hexane, UV) for some runs shows, in addition to the product at R_f = 0.36, a weak spot due to an intensely UV-active impurity at R_f = 0.41. The spectra are as follows: ^1H NMR (CDCl_3) δ : 2.45-2.58 (m, 4 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 5.87 (d, 1 H, J = 16), 6.96 (dt, 1 H, J = 16, 6); IR (CCl_4) cm^{-1} : (C=O) 1743 s, 1730 s, (C=C) 1661 m.

6. The submitters obtained tetravinyltin from Columbia Organic Chemicals Company; it was used as received. The checkers obtained it from K&K Laboratories, ICN Biomedicals Inc., Plainview, N.Y. It may also be synthesized by literature methods.⁴

7. Low-halide methyllithium in ether from Alfa Products, Morton/Thiokol, Inc. or Aldrich Chemical Company, Inc. was used as received. A single run using methyllithium/lithium bromide complex gave a significantly reduced yield (53%). Use of commercial vinylolithium in tetrahydrofuran gave a product contaminated with starting dimer, requiring chromatographic purification.

8. Copper(I) cyanide from Alfa Products, Morton/Thiokol, Inc. was used as received. *Caution! Copper(I) cyanide is severely toxic.* Care should be taken not to expose cyanide containing wastes to strong acid thus liberating hydrogen cyanide. Prior to disposal, insoluble wastes should be treated overnight with a strong alkaline solution containing calcium hypochlorite.

9. If the internal temperature is allowed to rise too quickly, rapid exothermic cuprate formation can occur with resultant decomposition of the reagent.

10. Tetramethyltin (bp 78°C) is a potentially hazardous side-product of this reaction. This work-up should therefore be done with gloves in a well-ventilated hood. Most of the tetramethyltin ends up in the condensate from the rotary evaporator; the condensate should be disposed of by incineration.

11. In two cases submitters have observed that the residue separated into two layers. The upper layer consists of a heavy oil apparently because of incomplete washing of the lithium suspension used in manufacturing methyllithium. When this happens it is necessary to remove the oil with a pipette prior to distillation. Failure to do so gives a product which appears pure by TLC, but which is substantially impure according to elemental analysis (1% high in carbon).

12. Submitters find that the product is homogeneous by TLC (30:70 ethyl acetate/hexane, I_2 , R_f = 0.43). Capillary column GLC analysis (30 m DB17 column, 120°C isothermal) is complicated by some thermal decarboxylation on the column. However, using a clean injection port liner and 180°C injection port, 95% of the product is eluted as a single, somewhat broad peak at 3.0 min retention time. The spectra are as follows: 1H NMR ($CDCl_3$) δ : 1.72 (m, 1 H), 2.1-2.6 (m, 3 H), 3.05 (d, 1 H, J = 11), 3.1-3.3 (m, 1 H), 3.75 (s, 3 H), 5.09 (d, 1 H, J = 11), 5.16 (d, 1 H, J = 17), 5.75-5.85 (m, 1 H); IR (CCl_4) cm^{-1} : (C=O) 1762 s, 1735 s, 1662 m, 1618 m; (C=C) 1644 w.

13. The submitters have carried out these steps on twice the scale given here. On that scale their yields for step A were 91-93%, for step B, 77-85%.

The checkers found that the diastereomeric purity of the product was much greater than 90% based upon its 300 MHz 1H and fully decoupled ^{13}C NMR spectra. Based on the proton-proton coupling constant (J = 11), trans geometry has been assigned.

3. Discussion

This procedure illustrates a general route to the 3-substituted 2-carbomethoxycyclopentanones, which are versatile intermediates for the preparation of a variety of cyclopentanoid products. For example, the product of this procedure, 2-carbomethoxy-3-vinylcyclopentanone, has been utilized in the synthesis of methyl dihydrojasmonate⁵ and 18-hydroxyestrone.⁶ This conjugate addition/cyclization approach (utilizing "Gilman reagents" prepared from copper(I) iodide) has been applied⁷ to the synthesis of the methyl, butyl, sec-butyl, neopentyl, and phenyl substituted 2-carbomethoxycyclopentanones. The present procedure takes advantage of the greater stability of

higher order cyanocuprates⁸ ("Lipshutz reagents") to overcome the moderate yield of the vinyl analogue due to cuprate decomposition as reported in earlier studies.⁷ With either the Gilman or Lipshutz reagents, Michael addition to dimethyl (E)-2-hexenedioate produces an enolate which undergoes Dieckmann cyclization faster than proton transfer. Therefore, no 4-substituted cyclopentanones are formed. This approach has now been extended to the synthesis of the corresponding cyclopentenones by using dimethyl 2-hexynedioate as the Michael acceptor.⁹

Alternatively, 3-substituted 2-carbomethoxycyclopentanones have been prepared by Michael addition to 2-carbomethoxycyclopentenone.¹⁰⁻¹² However, this Michael acceptor is unstable, difficult to prepare, and polymerizes in the presence of many nucleophiles.¹¹ A longer synthesis of 2-carbomethoxy-3-vinylcyclopentanone has been reported.⁵ The general route to 2-carbomethoxy-3-vinylcyclopentanones developed by Trost¹³ has the advantage of producing these compounds in optically active form.

Several catalyst systems have been described for the tail-to-tail dimerization of methyl acrylate.¹⁴⁻¹⁹ Advantages of the dimerization procedure described here are its mild conditions, efficient use of the catalyst, and high selectivity for the Δ^2 isomer. Tetrakis(acetonitrile)palladium tetrafluoroborate, $\text{Pd}(\text{NCMe})_4(\text{BF}_4)_2$, also efficiently catalyzes dimerization of ethyl acrylate and methyl methacrylate. The presence of lithium tetrafluoroborate in the reaction mixture increases the rate of the reaction and prolongs catalyst life. Dimerization of methyl acrylate can be effected without lithium tetrafluoroborate if the reaction is performed in nitromethane.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Carbomethoxy-3-vinylcyclopentanone: Cyclopentanecarboxylic acid, 2-ethenyl-5-oxo-, methyl ester (10); (75351-19-8)

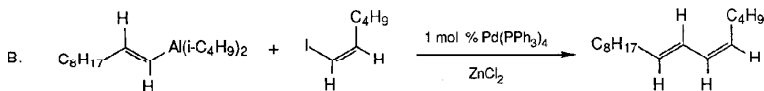
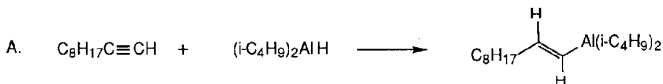
Dimethyl (E)-2-hexenedioate: 2-Hexenedioic acid, dimethyl ester, (E)- (10); (70353-99-0)

Methyl acrylate: 2-Propenoic acid, methyl ester (9); (96-33-3)

Tetrakis(acetonitrile)palladium tetrafluoroborate: Palladium(2+), tetrakis(acetonitrile)-, bis[tetrafluoroborate (1-)] (8,9); (21797-13-7)

PALLADIUM-CATALYZED SYNTHESIS OF CONJUGATED DIENES:

(5Z,7E)-5,7-HEXADECADIENE



Submitted by Ei-ichi Negishi, Tamotsu Takahashi, and Shigeru Baba.¹

Checked by Masako Ohta and Ryoji Noyori.

1. Procedure

Caution: Organoaluminum compounds are pyrophoric. They must be kept and used with caution under a nitrogen atmosphere.

A. *(E)*-1-Decenyldiisobutylalane. An oven-dried, 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen, immersed in a water bath kept at room temperature, and charged with 22.6 mL (125 mmol) of 1-decyne (Note 1) and 80 mL of hexane (Note 2). To this flask is added dropwise, with stirring, 22.3 mL (125 mmol) of diisobutylaluminum

hydride (Note 3) using a syringe (Note 4). After the addition has been completed, the water bath is replaced with an oil bath kept at 50-60°C, and the reaction mixture is stirred for 6 hr at this temperature (Note 5).

B. (5Z,7E)-5,7-Hexadecadiene. To a mixture of 21.0 g (100 mmol) of (Z)-1-hexenyl iodide (Note 6), 13.6 g (100 mmol) of zinc chloride (Note 7), and 1.15 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 8) in 100 mL of tetrahydrofuran (Note 9) is added the solution of (E)-1-decenyl-diisobutylalane prepared above, while the reaction temperature is controlled with a water bath at room temperature. After the reaction mixture is stirred for 6 hr at room temperature, it is slowly transferred into a mixture of 300 mL of ice-cooled 3 N hydrochloric acid and 100 mL of pentane via a double-ended needle under a positive pressure of nitrogen. The organic layer is separated, and the aqueous layer is extracted twice with 100 mL of pentane. The combined organic layer is washed with 100 mL of water, followed by 100 mL of saturated aqueous sodium bicarbonate, and then dried over anhydrous magnesium sulfate. After filtration, the solvent is removed using a rotary evaporator. Hydroquinone (30 mg) is added and the residue is distilled (Note 10) to give 14.3-15.8 g (64-66% based on (Z)-1-hexenyl iodide) of (5Z,7E)-5,7-hexadecadiene as a colorless liquid, bp 116-119°C (1 mm) (Notes 11, 12).

2. Notes

1. The submitters used 1-decyne from Farchan Laboratories, Inc., without further purification. The checkers used the material purchased from Aldrich Chemical Company, Inc. and Tokyo Kasei Kogyo Company.

2. Hexane available from Fisher Scientific Company was purified by distillation from sodium. The checkers used the solvent from Wako Pure Chemical Industries, Ltd. after distillation from sodium and benzophenone or calcium hydride under argon.

3. The submitters used neat diisobutylaluminum hydride obtained from Ethyl Corporation. The checkers used the material from Aldrich Chemical Company, Inc.

4. The submitters used a 50-mL syringe with a Luer-lock and a long (> 6 inch) 18 gauge needle, the plunger of which was lightly greased with a silicone grease. For a larger scale operation, it is advisable to use a septum-capped graduated cylinder and a double-ended needle in place of a syringe.

5. GLC analysis of a small aliquot after iodinolysis with iodine dissolved in tetrahydrofuran indicated the formation of (E)-1-decenyl-diisobutylalane (ca. 80%), 1-decynyl-diisobutylalane (7-8%), and 1-decene (5%), together with 1-decyne (ca. 10%).

6. (Z)-1-Hexenyl iodide was prepared by treating acetylene with lithium dibutylcuprate followed by iodine according to an *Organic Syntheses* procedure.²

7. Zinc chloride available from Mallinckrodt, Inc., was flame-dried under a slow stream of nitrogen. The checkers used the material from Wako Pure Chemical Industries, Ltd., after heating under vacuum (1 mm).

8. Tetrakis(triphenylphosphine)palladium was prepared according to an *Inorganic Syntheses* procedure.³ The submitters used a freshly prepared, shiny yellow crystalline sample of the palladium complex. On standing for an extended period of time ($>$ a few weeks), its color gradually darkens. The checkers used tetrakis(triphenylphosphine)palladium purchased from Aldrich Chemical Company, Inc.

9. Tetrahydrofuran available from Fisher Scientific Company or Wako Pure Chemical Industries, Ltd. was distilled from sodium and benzophenone.

10. Hydroquinone was added to avoid polymerization of the diene product.

11. Gas chromatographic examination of the reaction mixture using a 2-ft column of 20% SE-30 on Chromosorb W with undecane as an internal standard (200°C) indicates that (bZ,7E)-5,7-hexadecadiene is formed in 86-90% yield, based on (Z)-1-hexenyl iodide. The product obtained by this procedure shows the following properties: n_D^{23} 1.4662; IR (neat) cm^{-1} : 1630 (w), 1370 (w), 978 (m), 943 (m), 720 (m); ^1H NMR [CCl_4 , $(\text{CH}_3)_4\text{Si}$] δ : 0.8-1.0 (m, 6 H), 1.15-1.5 (m, 16 H), 1.9-2.3 (m, 4 H), 5.15 (dt, 1 H, $J = 10, 8$), 5.61 (dt, 1 H, $J = 14, 7$), 5.92 (dd, 1 H, $J = 10, 11$), 6.30 (dd, 1 H, $J = 11, 14$).

12. (5E,7E)-5,7-Hexadecadiene can be prepared in the same manner as described except that (E)-1-hexenyl iodide is used in place of its (Z) isomer. The (E) iodide is obtainable by treating (E)-1-hexenyldiisobutylalane, prepared from 1-hexyne and diisobutylaluminum hydride, with iodine in tetrahydrofuran.⁴ The (E,E) diene prepared by this procedure shows the following properties: n_D^{23} 1.4671; IR (neat) cm^{-1} : 1370 (w), 982 (m), 722 (m); ^1H NMR [CCl_4 , $(\text{CH}_3)_4\text{Si}$] δ : 0.89 (t, 6 H, $J = 6$), 1.15-1.7 (m, 16 H), 1.8-2.2 (m, 4H), 5.2-6.15 (m, 4 H); ^{13}C NMR [CDCl_3 , $(\text{CH}_3)_4\text{Si}$] δ : 13.93, 14.06, 22.34, 22.76, 29.40, 29.62, 31.16, 31.78, 32.03, 32.37, 32.72, 130.59, 132.19, 132.26.

3. Discussion

The procedure described here is based on two reports by Negishi and his co-workers.^{5,6} The original procedure⁵ did not use zinc chloride as the second catalyst and required ca. 5-mol % of $\text{Pd}(\text{PPh}_3)_4$. The preparation of

(E)-1-alkenylalane via hydroalumination was first reported by Wilke and Müller.⁷ The procedure used here is essentially that which was described by Zweifel.⁸

The first highly stereoselective and satisfactory syntheses of conjugated dienes of general applicability are those based on organoboron chemistry reported by Negishi for (E,E) dienes⁹ and (E,Z) dienes¹⁰ as well as by Zweifel for (Z,Z) dienes.¹¹

The method described here represents the first highly selective and general cross-coupling procedure for preparing conjugated dienes.^{5,6} Subsequently, several variations of the above-described method have been published by Negishi and others. Some salient features of these investigations are as follows. First, palladium-phosphine complexes, such as $\text{Pd}(\text{PPh}_3)_4$, are preferred to nickel complexes,⁵ which tend to reduce stereoselectivity. Second, all three possible stereoisomers may be prepared using this methodology. Third, in addition to Al,¹² Zr,¹² Mg,¹³ B,¹⁴ and Cu¹⁵ have been shown to participate in Pd-catalyzed alkenyl-alkenyl cross coupling. Fourth, the reaction is markedly accelerated by the addition of zinc and cadmium halides, such as ZnCl_2 , ZnBr_2 , and CdCl_2 ,⁶ at least in cases where organometals containing Al,⁶ Zr,⁶ and Cu¹⁵ are used. This and other observations suggest that alkenylzinc derivatives are probably the most reactive organometals in this reaction,⁶ although no systematic comparisons have so far been made. Otherwise, the choice of metal depends on the stereochemistry of the desired product, the required chemoselectivity, and other factors. For example, (E)-alkenyl metals are most directly available via hydroalumination,⁸ carboalumination,¹⁶ hydroboration,¹⁷ or hydrozirconation¹⁸ of alkynes. In cases where the use of such derivatives is desirable, Al, B, or Zr should be considered first. On the other hand, (Z)-

alkenyl metals are often readily available via carbocupration¹⁹ of alkynes, and they may be used directly or via formation of the corresponding (Z)-alkenyl iodide.

Together with the organoboron procedures mentioned above, the Pd-catalyzed cross coupling procedures have been applied to the synthesis of a wide variety of insect pheromones, terpenoids, and carotenoids.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Decyne (8,9); (764-93-2)

Diisobutylaluminum hydride: Aluminum, hydrodiisobutyl- (8); Aluminum, hydrobis(2-methylpropyl)- (9); (1191-15-7)

(Z)-1-Hexenyl iodide: 1-Hexene, 1-iodo-, (Z)- (8,9); (16538-47-9)

(E)-1-Hexenyl iodide: 1-Hexene, 1-iodo-, (E)- (8,9); (16644-98-7)

Tetrakis(triphenylphosphine)palladium: Palladium, tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

(E)-1-Hexenyldiisobutylalane: Aluminum, 1-hexenyldiisobutyl-, (E)- (8);

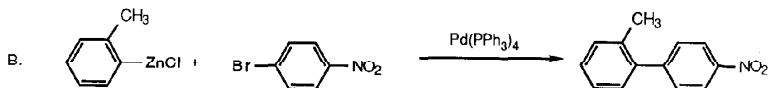
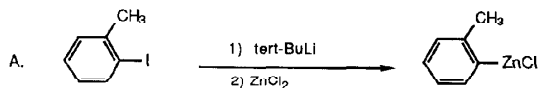
Aluminum, 1-hexenylbis(2-methylpropyl)-, (E)- (9); (20259-40-9)

1-Hexyne (8,9); (693-02-7)

SYNTHESIS OF BIARYLS VIA PALLADIUM-CATALYZED

CROSS COUPLING: 2-METHYL-4'-NITROBIPHENYL

(1,1'-Biphenyl, 2-methyl-4'-nitro-)



Submitted by Ei-ichi Negishi, Tamotsu Takahashi, and Anthony O. King,¹

Checked by Koji Kawai and Ryoji Noyori.

1. Procedure

A. *o*-Tolylzinc chloride. An oven-dried, 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, dropping funnel, rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen, immersed in a dry-ice bath kept at -78°C , and charged with 26.2 g (120 mmol) of *o*-iodotoluene (Note 1) and 60 mL of ether (Note 2). To this solution is added dropwise, with stirring, 154 mL (1.56 M, 240 mmol) of a hexane solution of *tert*-butyllithium (Note 3). After the reaction mixture is stirred for 1 hr at -78°C , it is warmed to room temperature, stirred for 1 hr and concentrated under diminished pressure using a water aspirator (ca. 15 mm) until most of the volatile solvents are evaporated. To this concentrate is added 80 mL of tetrahydrofuran (THF) (Notes 4 and 5). The mixture is, in

turn, added to 16.3 g (120 mmol) of dry zinc chloride (Note 6) and 60 mL of tetrahydrofuran placed in a similarly-equipped, 500-mL flask using a 16-gauge double-ended needle under a slight positive pressure of nitrogen; the resulting mixture is stirred for 1 hr at room temperature.

B. *2-Methyl-4'-nitrobiphenyl*. To a mixture of 1.16 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 7), 100 mL of tetrahydrofuran and 20.2 g (100 mmol) of 1-bromo-4-nitrobenzene (Note 8) in a 500-mL flask, set up as described above and immersed in a water bath, is added the *o*-tolylzinc chloride solution prepared above. The reaction mixture is stirred for 6 hr at room temperature and poured onto a mixture of 100 mL of ether and 300 mL of ice-cold 3 N hydrochloric acid. The organic layer is separated, and the aqueous layer is extracted with two 100-mL portions of ether. The combined organic layer is washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. After filtration, the solvent is removed using a rotary evaporator to give a light brown solid. The solid is recrystallized from 300 mL of hexane to yield 16.0 g of yellow crystals. The second crop from 50 mL of hexane is 2.4 g. The combined product is recrystallized from 100 mL of ethanol to afford 16.0 g of light yellow needles. Crystallization of the mother liquor from 25 mL of ethanol gives a second crop of 0.5 g. The total yield of 2-methyl-4'-nitrobiphenyl is 16.5 g (78% based on 1-bromo-4-nitrobenzene) (Note 9).

2. Notes

1. The submitters used *o*-iodotoluene from Aldrich Chemical Company, Inc. The checkers purchased it from Wako Chemical Industries, Ltd.

2. Ether available from Fisher Scientific Company or Sanraku Company was distilled from sodium and benzophenone.
3. The submitters used *tert*-butyllithium from Aldrich Chemical Company, Inc. after titration by the method of Watson and Eastham.^{2a} The checkers titrated it by the method of Lipton.^{2b}
4. Tetrahydrofuran from Fisher Scientific Company or Kishida Chemical Company was distilled from sodium and benzophenone.
5. Although somewhat more cumbersome, the following more economical procedure using lithium metal may also be used to generate *o*-tolyllithium. To 1.7 g (240 mg-atom) of freshly cut lithium in 35 mL of ether at 0°C is added dropwise 20.5 g (120 mmol) of *o*-bromotoluene in 25 mL of ether. After formation of *o*-tolyllithium, it is diluted with 60 mL of tetrahydrofuran before use.
6. Zinc chloride, available from Mallinckrodt, Inc., was flame-dried under a slow stream of nitrogen in the reaction flask. The checkers used zinc chloride from Wako Pure Chemical Industries, Inc. after fusion by flame-drying under reduced pressure for 20 min.
7. Tetrakis(triphenylphosphine)palladium was prepared according to the procedure of Coulson.³
8. The submitters used 1-bromo-4-nitrobenzene from Aldrich Chemical Company, Inc. without further purification. The checkers purchased it from Tokyo Kasei Kogyo Company.
9. Gas chromatographic examination of another reaction mixture run on a 10-mmol scale with undecane as an internal standard indicates that 2-methyl-4'-nitrobiphenyl is formed in 90% yield based on 1-bromo-4-nitrobenzene. The product obtained by this procedure shows the following properties: mp 99-101°C (lit.,⁴ mp 103-105°C); IR (neat) cm^{-1} : 1600 (s), 1510 (s), 1480 (s), 1340 (s).

858 (s), 778 (s), 756 (s), 730 (s), 702 (s); ^1H NMR (90 MHz, CDCl_3) δ : 2.26 (s, 3 H), 7.15-7.40 (m, 4 H), 7.48 (d, 2 H, $J = 8.5$), 8.27 (d, 2 H, $J = 8.5$); ^{13}C NMR (22.5 MHz, CDCl_3) δ : 20.30, 123.42, 126.16, 128.50, 129.42, 130.11, 130.75, 135.09, 139.67, 147.00, 148.85.

3. Discussion

The procedure described above is based on a paper reporting the Ni- or Pd-catalyzed reaction of arylzinc derivatives with aryl halides.⁵ The Ni- or Pd-catalyzed cross coupling reaction⁶ represents one of the most general and satisfactory routes to unsymmetrical biaryls.

The currently available data, such as those summarized in Table I, indicate the following. First, Ni-phosphine and Pd-phosphine complexes may be used interchangeably in many cases (Entries 1 and 2). In cases where sterically hindered aryl reagents, such as mesitylzinc chloride, are used, Ni catalysts tend to lead to higher product yields than the corresponding Pd catalysts (Entries 11 and 12). The scope with respect to the halogen leaving group of aryl halides is broader with Ni catalysts than with Pd catalysts. As a general rule, Ni-catalyzed aryl-aryl cross coupling proceeds smoothly with both aryl iodides and aryl bromides, whereas aryl bromides must be activated by an electron-withdrawing group in Pd-catalyzed cross coupling. Palladium-catalyzed cross coupling, however, is considerably more chemoselective than Ni-catalyzed cross coupling. Thus, for example, the nitro group appears to be totally incompatible with Ni-phosphine catalysts (Entry 9), and the presence of an alkynyl group tends to lower significantly the yield of product.

Second, the choice of metal counterion is of critical importance. Except in some special cases, alkali metals such as Li, Na, and K are unsatisfactory, partly because arylmetals which contain these metals readily participate in halogen-metal exchange leading to cross-homo scrambling,⁵ and also because these organometals are among the least chemoselective. Zinc appears to be among the most satisfactory metals from the standpoint of (a) product yield, (b) cross/homo ratio, (c) chemoselectivity, and (d) ease of preparation of arylmetal reagents, although Mg has also been used successfully in many cases.⁷ Results shown in Entries 11 and 13 indicate that the mesitylmagnesium reagent, generated in situ by treatment of mesityllithium with magnesium bromide, appears to be considerably inferior to mesitylzinc chloride generated in a similar manner. On the other hand, mesitylmagnesium bromide generated by treatment of mesityl bromide with Mg is as effective as mesitylzinc chloride (Entry 14). However, the yield of mesitylmagnesium bromide itself is in the range 50-60% and is substantially lower than that of mesitylzinc chloride (ca. 90%). Recent results obtained with arylboron derivatives⁸ appear highly promising, although the preparation of arylboronic acids is, at present, more elaborate than that of Grignard reagents or in situ generation of arylzinc reagents. Various other metals, such as Cd,⁹ Hg,¹⁰ Al,⁵ Sn,¹⁰ Zr,⁹ and Cu,¹⁰ have been shown to participate in aryl-aryl cross coupling. Their advantages over Zn or Mg are, however, largely unknown.

Third, the procedure described above has been applied to the preparation of various biaryls containing hetero-aromatic rings (Entries 15-17, 19, 20). Although the number of papers reporting the use of the Ni- or Pd-catalyzed procedure for aryl-aryl coupling is still small, the synthesis of steganone by Raphael and his co-workers¹¹ is demonstrative of its synthetic potential.

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TABLE I
PREPARATION OF BIARYLS BY THE Ni- OR Pd-CATALYZED REACTION OF
ARYLMETALS WITH ARYL HALIDES^a

Entry	Ar ¹ M ^b	ArX	Catalyst ^c	Amount (%)	Yield ^d (%)
1	PhZnCl	p-Iodoanisole	Ni	5	85
2	PhZnCl	p-Iodoanisole	Pd ^e	5	87
3	PhMgBr	p-Iodoanisole	Pd ^e	5	71
4	PhAl(i-Bu) ₂	p-Iodoanisole	Pd ^e	5	72
5	PhZnCl	p-BrC ₆ H ₄ CN	Ni	5	90
6	PhZnCl	p-BrC ₆ H ₄ COOMe	Ni	5	70
7	PhZnCl	p-IC ₆ H ₄ NO ₂	Pd ^e	5	90 (74)
8	o-TolZnCl	p-BrC ₆ H ₄ NO ₂	Pd ^e	1	90 (70)
9	o-TolZnCl	p-BrC ₆ H ₄ NO ₂	Ni	1	0
10	m-TolZnCl	m-IC ₆ H ₄ CH ₃	Ni	5	95
11	MesZnCl ^f	o-IC ₆ H ₄ CH ₃	Ni	5	93
12	MesZnCl	o-IC ₆ H ₄ CH ₃	Pd	5	88
13	MesMgBr ^g	o-IC ₆ H ₄ CH ₃	Ni	5	38
14	MesMgBr	o-IC ₆ H ₄ CH ₃	Ni	5	92
15	PhZnCl	2-Furyl iodide	Pd	5	91
16	2-FurylZnCl	PhI	Pd	5	94 (89)
17	3-FurylZnCl	PhI	Pd	5	89 (85)
18	PhZnCl	2-Furyl bromide	Pd	5	0
19	2-ThienylZnCl	PhI	Pd	5	81 (75)
20	PhZnCl	2-Pyridyl bromide	Pd	5	99 (89)
21	PhZnCl	3-Pyridyl bromide	Pd	5	0

^aThe reactions are carried out in THF at room temperature. The time required for completion is usually less than several hours. ^bUnless otherwise mentioned, arylzinc chlorides and arylalanes are prepared via in situ transmetalation of aryllithiums, while arylmagnesium halides are prepared by treating aryl halides with Mg. The molar ratio of an aryl metal to an aryl halide is 1-1.5. ^cNi - Ni(PPh₃)₄ prepared in situ by the reaction of Ni(acac)₂, PPh₃, and (i-Bu)₂AlH (1:4:1). Unless otherwise indicated, Pd = Pd(PPh₃)₄. ^dBy GLC. The numbers in parentheses are isolated yields. ^eThe Pd catalyst is prepared by treating Cl₂Pd(PPh₃)₂ with (i-Bu)₂AlH (2 equiv). ^fMes = mesityl. ^gGenerated in situ by treating MesLi with MgBr₂ generated from 1,2-dibromoethane and Mg.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

4-Methyl-4'-nitrobiphenyl: Biphenyl, 2-methyl-4'-nitro- (8); 1,1'-Biphenyl, 2-methyl-4'-nitro- (9); (33350-73-1)

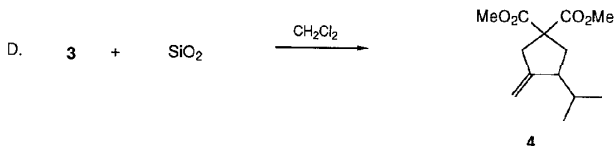
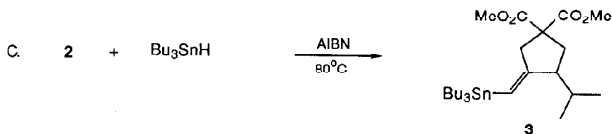
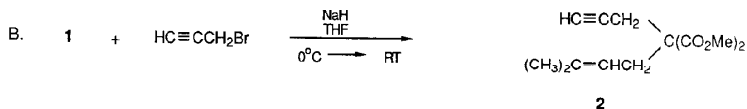
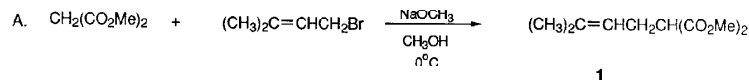
o-Tolylzinc chloride: Zinc, chloro(2-methylphenyl)- (11); (84109-17-1)

o-Iodotoluene: Toluene, o-iodo- (8); Benzene, 1-iodo-2-methyl- (9); (615-37-2)

Tetrakis(triphenylphosphine)palladium: Palladium,

tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

VINYL RADICAL CYCLIZATION VIA ADDITION OF TIN RADICALS TO TRIPLE BONDS



Submitted by Robert Mook, Jr. and Philip Michael Sher.¹

Checked by Anthony G. Schaefer and Leo A. Paquette.

1. Procedure

A. *(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester (1)*. To a 500-mL, flame-dried, three-necked, round-bottomed flask under an argon atmosphere and fitted with a thermometer, pressure-equalizing addition funnel and a

magnetic stirring bar, is added 250 mL of methanol (Note 1). The flask is immersed in an ice bath, and 6.7 g (0.29 mol) of sodium is added cautiously (Note 2). After the sodium has dissolved, the ice bath is removed, 36.9 g (0.28 mol) of dimethyl malonate (Note 1) is added at room temperature, and the solution is stirred for 0.5 hr. The reaction mixture is cooled to 0°C, and 45.8 g (0.31 mol) of 3,3-dimethylallyl bromide (Note 1) is added dropwise while the temperature is maintained near 5°C (Note 3). After 1 hr (Note 4), the reaction mixture is transferred to a 1-L, one-necked, round-bottomed flask with the aid of a small amount of methanol and concentrated with a rotary evaporator. The white residue is taken up in 400 mL of ether and 300 mL of a saturated salt/saturated sodium bicarbonate (1:1) solution and is transferred to a separatory funnel. The ether layer is separated, and the aqueous layer is extracted with ether (1 x 200 mL). The ether layers are combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. Distillation of the residue through a 6-inch Vigreux column (after a small fore-run is collected) yields 43.9-44.5 g (78-79%) of 1, bp 60-63°C (0.15 mm) (Note 5).

B. *(3-Methyl-3-butonyl)(3-propynyl)propanedioic acid, dimethyl ester* (2). To a 1-L, flame-dried, three-necked, round-bottomed flask, equipped with a magnetic stirring bar (Note 6) and under an argon atmosphere, is added 9.0 g (0.19 mol) of sodium hydride dispersion (Note 7). The sodium hydride is washed with petroleum ether (4 x 30 mL), removing the petroleum ether by pipette after the sodium hydride has settled. The flask is then fitted with a thermometer and an oven-dried pressure-equalizing addition funnel and charged with 500 mL of tetrahydrofuran (Note 7). The heterogeneous mixture is cooled with an ice bath, and 36.4 g (0.18 mol) of the monoalkyl diester (1) is added dropwise at the rate of 1 drop/2-3 sec (Note 2). The cooling bath is removed

when the addition is complete, and the solution is stirred until no more gas evolves (approximately 1 hr). The reaction mixture is recooled to 0°C, and 22 ml of propargyl bromide solution (0.20 mol) (Note 7) is added dropwise while the temperature is maintained at 0-10°C. Sodium bromide begins to precipitate within 20 min. The ice bath is removed, and the reaction mixture is stirred overnight (Note 8). After careful addition of 50 mL of water (Note 9) and removal of the stirring bar, the solution is transferred to a 1-L, one-necked, round-bottomed flask and concentrated with a rotary evaporator. The residue is taken up in 500 ml of ether and washed with water (3 x 300 ml) and saturated salt solution (1 x 100 mL). The aqueous layers are combined, saturated with salt, and extracted with ether (2 x 150 mL). The ether layers are combined, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue is distilled through a short path distillation apparatus at 80°C (0.25 mm) to yield 34.0-34.2 g (79-80%) of 2 (Note 10).

C. (Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester (3). A flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with argon, and 23.8 g (0.100 mol) of dialkylmalonate diester (2), 30.2 g (< 0.104 mol) of tributyltin hydride (Note 11), and 40 mg (0.25 mmol) of azobisisobutyronitrile (AIBN) (Note 12) are added neat (Notes 13, 14). The entire assembly is lowered into an oil bath maintained at 75-85°C, and the mixture is stirred. After an induction period of less than 30 min, an exothermic reaction occurs which produces a small amount of gas and a rise in the temperature of the oil bath (as much as 20°C for a small bath). After this point TLC shows that the reaction is essentially complete (Notes 15, 16, 17). Unpurified 3 thus obtained is suitable for protodestannylation.

D. *3-Methylene-4-isopropyl-1,1-cyclopentenedicarboxylic acid, dimethyl ester* (4). Crude vinylstannane (3) is transferred to a 2-L Erlenmeyer flask which contains 1 L of dichloromethane, 350 g of silica (Note 18), and a large (7 cm x 3 cm egg-shaped) stirring bar. The flask is stoppered, and the mixture is stirred for 24-48 hr (Note 19). The mixture is divided into three portions. Each portion is filtered under reduced pressure with a 600-mL glass frit, and the silica is washed with ethyl acetate (8 x 200 mL) to extract all of the desired product (Note 20). The solution is filtered through Celite and the solvent is removed with a rotary evaporator. Distillation through a short path distillation apparatus (with no forerun) gives 19.8-20.5 g of 4, (83-85% overall from 2), bp 80°-85°C (0.2 mm) (Note 21).

2. Notes

1. The use of less solvent can result in gel formation. Methanol was freshly distilled from calcium hydride or magnesium metal. Dimethyl malonate (Aldrich Chemical Company, Inc.) was distilled before use. 3,3-Dimethallyl bromide may be purchased from Aldrich Chemical Company, Inc. or Wiley Organics.

2. The apparatus should be vented. Hydrogen gas formation causes vigorous bubbling.

3. At higher temperatures more dialkylation occurs.

4. The reaction can be monitored by TLC eluting with 10% ethyl acetate/petroleum ether.

5. The physical properties are as follows: IR (neat) cm^{-1} : 2980, 1730-1760, 1435, 1040; ^1H 200 MHz NMR (CDCl_3) δ : 1.62 (s, 3 H), 1.65 (s, 3 H), 2.56 (t, 2 H, $J = 7$), 3.34 (t, 1 H, $J = 7$), 3.70 (s, 6 H), 5.06 (bt, 1 H, $J = 7$).

6. Unless a sufficiently large stirring bar is used, the precipitate may be impossible to stir. An overhead mechanical stirrer can be substituted.
7. Sodium hydride, 50% oil dispersion, was purchased from Alfa Products, Morton/Thiokol Inc. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Propargyl bromide (80% in toluene) was purchased from Aldrich Chemical Company, Inc. and used directly.
8. The reaction is generally complete sooner, but because its progress is difficult to monitor by TLC (since the starting material and product have similar R_f s) the submitters routinely allow more than enough time.
9. Trace amounts of sodium hydride may still be present. If the water is added too quickly a vigorous reaction results.
10. The checkers observed a boiling point of 99–100°C (0.35 mm) for this material. The physical properties are as follows: IR (neat) cm^{-1} : 3290, 2960, 1740, 1440; ^1H 300 MHz NMR (CDCl_3) δ : 1.61 (s, 3 H), 1.65 (s, 3 H), 1.97 (t, 1 H, $J = 3$), 2.7 (m, 4 H), 3.69 (s, 6 H), 4.9 (t, 1 H, $J = 7$).
11. Tributyltin hydride, 97%, was purchased from Aldrich Chemical Company, Inc. and used directly. A minimal excess of this reagent is desired in order to ensure clean distillation of 4. If the product is to be purified by chromatography, a 10% excess of tributyltin hydride can be used.
12. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical Company, Inc. and recrystallized from chloroform. To exclude the possibility of a violent reaction, no more than twice this amount should be used on this scale.
13. These reactions can also be run in benzene, which is preferable in cases where transfer of hydrogen to the vinyl radical is competitive with cyclization.

14. The submitters routinely interposed a Vigreux column between the reaction flask and the argon line to protect the argon line in the event of bumping.

15. The reaction mixture is routinely stirred hot for an additional 30 min to ensure complete conversion.

16. Vinylstannane (3) may protodestannylate on TLC, which could be confusing when monitoring reaction C since dialkylmalonate diester (2) and protodestannylated product (4) have similar R_f s. The submitters found that TLC plates stored in the open air (as opposed to desiccator-stored plates) caused negligible protodestannylation.

17. Although vinylstannane 3 protodestannylates on silica, it may be isolated by flash chromatography in greater than 90% yield: IR (neat) cm^{-1} : 2960, 2930, 2880, 2860, 1740, 1615, 1465, 1435; ^1H 200 MHz NMR (CDCl_3) δ : 3.71 (s, 3 H), 3.73 (s, 3 H), 5.62 (bs, 1 H) with satellites.

18. The submitters employed Silica Woelm 32-63 purchased from Universal Scientific, Inc.; the checkers used Merck silica gel 60 (40-60 μm in size). Before use the silica was oven dried for several days at 160°C. Undried silica may be used, but larger quantities and/or longer reaction times are necessary.

19. TLC plates stored in the open air should be used (see Note 16) to monitor reaction D accurately. Approximately 4% of noncyclized hydrostannylation product is produced in reaction C. This material forms co-spots with 3 (2.5% ethyl acetate in petroleum ether), but protodestannylates much more slowly. Therefore, by TLC reaction D may appear not to go to completion.

20. A larger glass frit would obviate division of the mixture. In any case, the silica should be washed until by TLC the filtrate no longer contains 4.

21. The checkers observed a boiling point of 98-105°C (0.35 mm) for this product: IR (neat) cm^{-1} : 3080, 2960, 2875, 1735, 1655, 1435, 1385, 1365, 890. MS (CI) $M + 1 = 241$; ^1H 300 MHz NMR (CDCl_3) δ : 0.75 (d, 3 H, $J = 7$), 0.85 (d, 3 H, $J = 7$), 1.80 (m, 2 H), 2.40 (m, 2 H), 2.84 (m, 2 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 4.72 (bs, 1 H), 4.90 (bs, 1 H).

3. Discussion

Free radical reactions are proving to be synthetically useful alternatives for producing carbon-carbon bonds.^{2,3} Recently, Stork has shown that vinyl radicals are valuable in ring forming reactions since they place a double bond in a predictable position.³ Their compatibility with many unprotected functional groups and their ability to form quaternary centers are additional features which make vinyl radical cyclization an attractive synthetic method.

Previously, vinyl radicals for cyclization reactions were produced by the reduction of vinyl halides with tributyltin hydride. In the present procedure, vinyl radicals are produced by the addition of tin radicals to triple bonds.⁴ These vinyl radicals undergo cyclization in an analogous fashion to those generated from vinyl halides. However, this approach provides vinylstannanes stereoselectively; these vinylstannanes may be utilized in a wide range of synthetic transformations.

Vinylstannanes⁵ are versatile synthetic intermediates. They serve as a source of stereospecific vinyl anions and vinyl cuprates.^{5a,d,6} In the presence of Pd(0), vinylstannanes can be acylated^{7a,b} or alkylated.^{7c,d} Epoxidation followed by rearrangement converts vinylstannanes into carbonyl compounds.⁸ Treatment with halogens or N-halosuccinimides yields vinyl halides.^{5a-d,6c,9} Deuterium labeled olefins result from deuteration of vinyl stannanes with AcOD or DCl.^{5d} Olefins identical to those produced in vinyl halide reductions are obtained on protodestannylation with silica gel, which, unlike simple acid treatment, solves the problem of separation from tin residues.¹⁰

Many examples of radicals kinetically favoring addition to double bonds over triple bonds are known.¹¹ Yet, vinyl radical cyclization in the present procedure is initiated by the addition of a tin radical to a triple bond.¹² The apparent selectivity of the tin radical for the triple bond in the presence of a double bond is, at least in some cases, a result of reversible addition to both followed by selective cyclization of the vinyl radical.⁴

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12. The sterically less biased case of allylpropargyl malonate gives greater than 75% of analogous product.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester: Propanedioic acid, (3-methyl-2-butenyl)-, dimethyl ester (9); (43219-18-7)

Methanol (8,9); (67-56-1)

Sodium (8,9); (7440-23-5)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

3,3-Dimethylallyl bromide. 2-Butene, 1-bromo-3-methyl- (8,9); (870-63-3)

Sodium hydride (8,9); (7646-69-7)

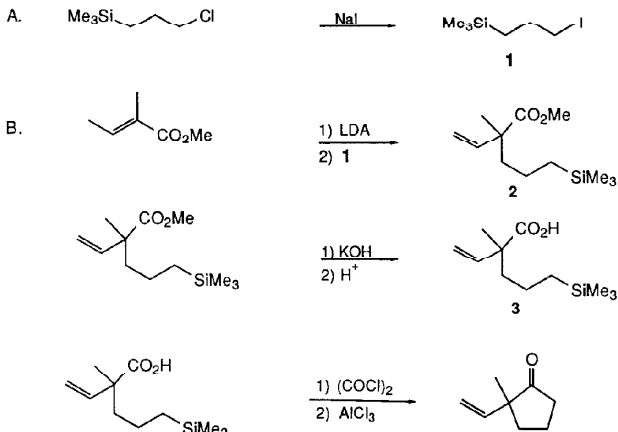
Propargyl bromide: Propyne, 3-bromo- (8); 1-Propyne, 3-bromo- (9); (106-96-7)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

Azobisisobutyronitrile: Propionitrile, 2,2' azobis[2 methyl- (8);

Propanenitrile, 2,2'-azobis[2-methyl- (9); (78-67-1)

**CYCLOPENTANONES FROM CARBOXYLIC ACIDS VIA INTRAMOLECULAR
ACYLATION OF ALKYL-SILANES: 2-METHYL-2-VINYLCYCLOPENTANONE**
(Cyclopentanone, 2-ethenyl-2-methyl-)



Submitted by Isao Kuwajima and Hirokazu Urabe.¹

Checked by Robert J. Ross and Leo A. Paquette.

1. Procedure

Caution! The following reactions should be performed in an efficient hood.

A. *1-Iodo-3-trimethylsilylpropane.* In a dry, 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and rubber septum is placed 15.0 g (0.10 mol) of sodium iodide. A nitrogen inlet tube is connected to the top of the reflux condenser and all the apparatus is kept under nitrogen. To this vessel are added 50 mL of acetone and 11.5 mL

(10 g, 0.066 mol) of 1-chloro-3-trimethylsilylpropane (Note 1) with a hypodermic syringe through the septum; the resulting white suspension is stirred under reflux for 24 hr. The condenser is replaced with a Claisen head, and the bulk of the solvent is removed under ordinary pressure (Note 2) to give a white slurry. To this is added 60 mL of hexane and the inorganic salts are filtered off by suction. The filter cake is washed with five 10-mL portions of hexane. The hexane is distilled off from the combined organic portions at atmospheric pressure. The residual oil is transferred to a 50-mL, round-bottomed flask fitted with a stirring bar and a Claisen head, and distilled under reduced pressure to afford 1-iodo-3-trimethylsilylpropane 1 (11.5-13.1 g, 72-81%), bp 84-86°C (25 mm), as a clear liquid (Notes 3 and 4).

B. 2-Methyl-2-vinylcyclopentanone. A 300-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, nitrogen inlet tube, and rubber septum is kept under dry nitrogen. To this flask are introduced 8.3 mL (5.99 g, 0.0591 mol) of diisopropylamine and 120 mL of tetrahydrofuran (Note 5) with a syringe through the septum. The flask is cooled in a dry ice-hexane bath. To the solution is slowly added 38.7 mL of butyllithium (1.53 M in hexane, 0.0592 mol) with a syringe and the mixture is kept at 0°C (in an ice bath) for 10 min. The resulting solution of lithium diisopropylamide is again cooled in a dry ice-hexane bath (-78°C), and 11.2 mL (11.57 g, 0.0645 mol) of hexamethylphosphoric triamide (HMPA) (Note 6) is added. After stirring for 30 min, 6.47 mL (6.15 g, 0.0539 mol) of methyl tiglate is injected drop by drop at -78°C. After the solution is stirred for an additional 20 min, 13.0 g (0.0537 mol) of 1-iodo-3-trimethylsilylpropane 1 is added with a syringe and the dry ice-hexane bath is replaced with an ice bath. The solution is stirred at about 0°C for 1 hr and then poured onto 150 mL of ice-cooled 3 N hydrochloric acid covered with 150 mL of hexane. The organic layer is

separated and the aqueous layer is extracted with two 80-mL portions of hexane. The combined organic layers are washed successively with 50 mL of 3 N hydrochloric acid and 50 mL of saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvent is removed on a rotary evaporator to afford the crude ester 2 (ca. 13 g) (Note 7) which is sufficiently pure for the next operation.

In a two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and reflux condenser, the top of which is fitted with a nitrogen inlet tube, is placed 7.3 g (ca. 0.13 mol) of 85% pure potassium hydroxide. To the flask are added 4 mL of water and an ethanol solution (60 mL) of the crude ester 2 (ca. 13 g) with a syringe; the mixture is refluxed for 1 hr. The reflux condenser is replaced with a Claisen head and the bulk of the solvent is distilled off over 30 min (Note 8). The residue is cooled in an ice bath and 80 mL of 6 N hydrochloric acid is cautiously introduced. The mixture is extracted with 150 mL of hexane and the organic layer is separated. To the aqueous layer is added 40 mL of concentrated hydrochloric acid and the solution is again extracted with two 100-mL portions of hexane. The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude acid 3 (10.6-12.0 g) as a dark-colored oil (Note 9).

A 200-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, reflux condenser, and rubber septum is flushed with nitrogen. To this flask is introduced a dry benzene solution (50 mL) of crude acid 3 through the septum. Then 8.9 mL (12.9 g, 0.101 mol) of oxalyl chloride is slowly added with stirring at room temperature. After the evolution of gas ceases, the solution is further heated in an oil bath maintained at 70°C for 10 min. The solvent, together with excess oxalyl chloride, is removed at room

temperature first on a rotary evaporator and finally with a vacuum pump to leave the crude acid chloride of 3 as a dark-colored oil (Note 10).

In a 300-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet tube, dropping funnel, and rubber septum are placed 7.45 g (0.0559 mol) of powdered aluminum chloride and a magnetic stirring bar. After 100 mL of dichloromethane (Note 11) is introduced, the crude acid chloride, dissolved in 50 mL of dichloromethane, is added via the dropping funnel to the stirred suspension of aluminum chloride at 0°C over 5 min, whereupon most of the aluminum chloride dissolves. After further stirring at 0°C for 15 min and at room temperature for 15 min, the flask is recooled in an ice bath and 100 mL of 3 N hydrochloric acid is cautiously added through the dropping funnel. The organic phase is separated and the aqueous layer is extracted three times with 50-mL portions of dichloromethane. The combined organic layers are successively washed with 30 mL of 3 N hydrochloric acid and 50 mL of saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvent is removed under ordinary pressure and the residue is distilled under reduced pressure to give 2-methyl-2-vinylcyclopentanone as a clear liquid (3.74-5.6 g, 56-84% yield based on the methyl tiglate), bp 104-124°C (110 mm) (Note 12), ca. 95% pure by GLC (Note 13).

2. Notes

1. 1-Chloro-3-trimethylsilylpropane, obtained from Petrarch Systems, Inc., was used as received.
2. About 40 mL of distillate is collected.

3. 1-Iodo-3-trimethylsilylpropane has the following spectral properties: ^1H NMR (CCl_4 , 3% benzene (δ 7.24) as an internal standard) δ : -0.03 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 0.34-0.74 (m, 2 H, CH_2Si), 1.47-2.04 (m, 2 H, CH_2), 3.07 (t, 2 H, $J = 7$, CH_2I); IR (neat) cm^{-1} : 2950, 1250, 860, 830.

4. 1-Iodo-3-trimethylsilylpropane can also be prepared by other methods: See reference 2.

5. Tetrahydrofuran was used after distillation from sodium benzophenone ketyl under nitrogen.

6. It was found by the checkers that N,N'-dimethylpropyleneurea (DMPU),³ supplied by Aldrich Chemical Company, Inc. or Fluka, can be substituted for HMPA with no change in either procedure or yield.

7. Alkylation of methyl tiglate was carried out according to a reported procedure.⁴

8. About 50 mL of distillate was collected.

9. Crude 3 exhibited the following spectral properties, which are virtually identical with those of an analytically pure sample: ^1H NMR (CCl_4 , 3% benzene (δ 7.24) as an internal standard) δ : 0.16 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 0.44-0.77 (m, 2 H, CH_2Si), 1.1-2.0 (m, 4 H, CH_2CH_2), 1.41 (s, 3 H, CH_3), 4.91-5.31 (m, 2 H, $\text{C}=\text{CH}_2$), 6.04 (d of d, 1 H, $J = 10$ and 18, $\text{CH}=\text{CH}_2$), 11.34 (s, 1 H, CO_2H); IR (neat) cm^{-1} : 2950, 1700, 1400, 1250, 1180, 920, 840, 740, 680.

10. Conversion of the carboxylic acid to the acid chloride was based on a reported method.⁵

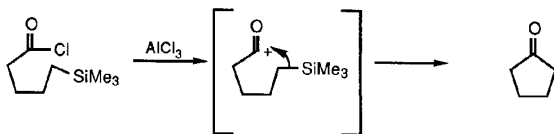
11. Dichloromethane was distilled from phosphorus pentoxide.

12. 2-Methyl-2-vinylcyclopentanone showed the following spectral properties: ^1H NMR (CCl_4) δ : 0.73 (s, 3 H, CH_3), 1.6-2.3 (m, 6 H, $(\text{CH}_2)_3$), 4.67-5.07 (m, 2 H, $\text{C}=\text{CH}_2$), 5.62 (d of d, 1 H, $J = 8$ and 18, $\text{CH}=\text{CH}_2$); IR (neat) cm^{-1} : 3070, 2950, 1730, 1640, 1450, 1400, 1150, 1060, 1040, 1000, 920.

13. Vapor phase chromatography was performed on an OV 101, fused silica, 20-m capillary column.

3. Discussion




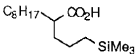

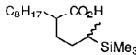

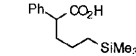

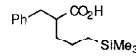

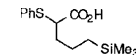

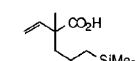

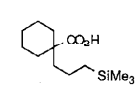

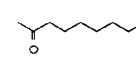
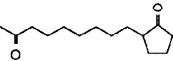
Cyclopentanones are widely found in natural products and are also useful intermediates in organic synthesis. Thus a facile construction of cyclopentanones from easily available acyclic precursors is particularly desirable. This method of preparation is based on an intramolecular acylation of 5-trimethylsilylalkanoyl chlorides previously reported by us.² The starting materials are generally prepared by alkylation of carboxylic acids with 3-trimethylsilylalkyl halides followed by their conversion to the corresponding acid chlorides. The cyclization of the acid chlorides proceeds cleanly with aluminum chloride. An acyl cation generated from the acid chloride and aluminum chloride is trapped with the alkyl-silicon bond in the same molecule to yield a cyclopentanone selectively (eq. 1).



Other results are collected in the Table,² which shows that cyclopentanones having a variety of substituents can be prepared according to this procedure with substantial advantage over other methods, e.g. alkylation of 2-alkoxycarbonylcyclopentanone.

TABLE

CYCLOPENTANONE SYNTHESIS BY INTRAMOLECULAR ACYLATION OF 5 TRIMETHYLSILYLALKANOYL CHLORIDES^a

 1	$\xrightarrow{(\text{COCl})_2}$	 2	$\xrightarrow{\text{AlCl}_3}$	 3
Acid (1)		Product (3)		Yield(%) ^b
				92 ^c
				83
				84
				85
				60 ^d
				67
				70
				76 ^e

^aReactions are carried out on 0.2-0.3-mmol scale with the reactant ratio 1/(COCl)₂/AlCl₃ = 1:2:1.^bOverall yield from 1. Products are isolated by chromatography.^cReaction on 3.5-mmol scale; the product was isolated by Kugelrohr distillation.^dReactant ratio: 1/(COCl)₂/AlCl₃ = 1:1.5:0.75.^eReactant ratio: 1/(COCl)₂/AlCl₃ = 1:2:2.

1. Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan.
2. Urabe, H.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 1140.
3. Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
4. Herrmann, J. L.; Kieczkowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.
5. Adams, R.; Ulich, L. H. *J. Am. Chem. Soc.* **1920**, *42*, 599.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Methyl-2-vinylcyclopentanone: Cyclopentanone, 2-ethenyl-2-methyl- (11);
(88729-76-4)

1-Iodo-3-trimethylsilylpropane: Silane, (3-iodopropyl)trimethyl- (9);
(18135-48-3)

1-Chloro-3-trimethylsilylpropane: Silane, (3-chloropropyl)trimethyl- (8,9);
(2344-83-4)

Hexamethylphosphoric triamide: Phosphoric triamide, hexamethyl- (8,9);
(680-31-9)

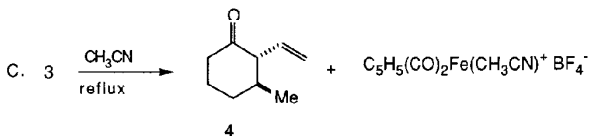
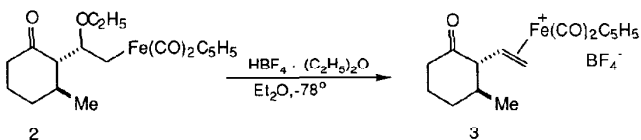
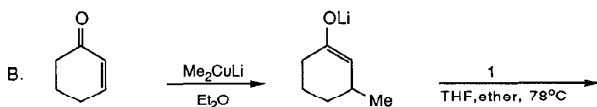
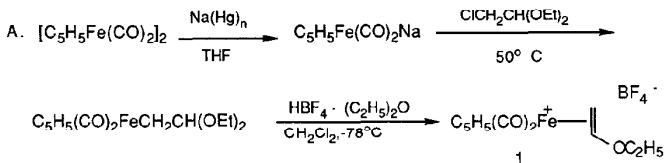
N,N'-Dimethylpropyleneurea: 2(1H)-Pyrimidone, tetrahydro-1,3-dimethyl- (8,9);
(7226-23-5)

Methyl tiglate: 2-Butenoic acid, 2-methyl-, methyl ester, (E)- (9);
(6622-76-0)

Oxalyl chloride (8); Ethanediol dichloride (9); (79-37-8)

VINYLATION OF ENOLATES WITH A VINYL CATION EQUIVALENT:

trans-3-METHYL-2-VINYLCYCLOHEXANONE



Submitted by Tony C. T. Chang,¹ Myron Rosenblum,² and Nancy Simms.²

Checked by Ed Fewkes and Martin F. Semmelhack.

1. Procedure

Caution! Care should be exercised in the preparation of the sodium amalgam since the initial reaction is highly exothermic. This and all subsequent operations should be carried out in a well-ventilated hood. Chloroacetaldehyde diethyl acetal is an irritant and a mutagen. Care should be exercised in its handling.

A. Dicarbonyl(cyclopentadienyl)(ethyl vinyl ether)iron tetrafluoroborate

1. A 500-mL, three-necked flask, with a stopcock at the bottom, is fitted with a nitrogen inlet and a mechanical stirrer with a Teflon paddle. Nitrogen is passed through the flask while it is flame-dried (Note 1) and then 70 mL of mercury is introduced. The mercury is stirred vigorously as 7.2 g (0.31 mol) of sodium metal, cut into small pieces, is slowly added, under a strong flow of nitrogen; after which the remaining neck is capped with a rubber septum. The amalgam is allowed to cool to room temperature and 100 mL of tetrahydrofuran is added (Notes 2 and 3). While the system is flushed with nitrogen, one septum is removed and 35.4 g (0.1 mol) of dicarbonyl(cyclopentadienyl)diiron $[(CO)_2CpFe]_2$ (Note 4) is added at once. Vigorous stirring is continued for 40 min. The mercury is drained through the stopcock, and the deep yellow-red solution of sodium dicarbonyl(cyclopentadienyl)ferrate, which is ready for use without further purification, is transferred (Note 2) to a 500-mL, round-bottomed flask containing a magnetic stirrer. An additional 50 mL of tetrahydrofuran is used to rinse the amalgam flask.

Chloroacetaldehyde diethyl acetal (31.11 g, 0.20 mol) (Note 5) is added by syringe slowly, since the initial reaction is exothermic. The resulting solution is heated at 50°C with stirring for 2 hr. After the solution is cooled to room temperature, solvent is removed, first with a rotary evaporator

and then with an oil pump overnight (Note 6). The residue is taken up in ethyl ether (Note 7), and filtered by suction through a 1 1/2-inch plug of Celite packed in a 250-mL coarse porosity, fritted Schlenk tube (Notes 8 and 9). The filtrate is collected in a 1-L, round-bottomed flask containing a magnetic stirring bar. The sodium chloride residue is washed several times with fresh ether until the washings are nearly colorless. The filter tube is removed and the flask is capped with a rubber septum and a nitrogen inlet; air is displaced by flushing the flask with nitrogen.

The solution is cooled to -78°C in a dry ice-acetone bath, and 38.19 g (0.23 mol) of tetrafluoroboric acid-diethyl ether complex (Note 10) is added dropwise by syringe over a 30-min period. The solution is allowed to warm to room temperature. The yellow precipitate is filtered off and collected in a 250-mL Schlenk tube, washed with ether, dried under a stream of nitrogen and finally under reduced pressure (oil pump). The bright yellow salt 1 weighs 43.2-57.6 g (60-80%) and may be used without further purification (Note 11). It may be stored indefinitely under nitrogen at 0°C without decomposition.

B. Dicarboxyl(cyclopentadienyl)(trans-3-methyl-2-vinylcyclohexanone)iron tetrafluoroborate 3. Under a nitrogen atmosphere, cuprous iodide (Note 12) (24.76 g, 0.13 mol) and 150 mL of ether are placed in a 1-L, three-necked, round-bottomed flask containing a magnetic stirring bar, and cooled to 0°C in an ice-salt bath. First 172 mL (0.26 mol) of methyllithium in ether (Note 13) is added by syringe, then 12.60 g (0.13 mol) of 2-cyclohexen-1-one (Note 14) is added dropwise by syringe while the mixture is stirred at 0°C . A bright yellow precipitate forms immediately. After 15 min, 200 mL of tetrahydrofuran is added and the mixture is cooled to -78°C in a dry ice-acetone bath. While vigorous stirring and a strong flow of nitrogen are maintained, one septum is removed and 43.70 g (0.13 mol) of complex salt 1 is added at once. The septum

is replaced and 50 mL of fresh tetrahydrofuran is used to wash solid 1 from the neck and sides of the reaction vessel. After 1 hr at -78°C , the mixture is allowed to warm to room temperature while stirring is continued. Stirring is halted to allow insoluble copper salts to settle leaving a red supernatant liquid. A 250-mL, coarse-frit, Schlenk filter is prepared with a Celite mat, topped with 2 inches of activity-IV neutral alumina (Note 15), which is further deactivated by washing in the Schlenk tube with 100 mL of diethyl ether. The supernatant solution is transferred to the Schlenk tube by cannula and filtered by suction into a 1-L, round-bottomed flask containing a magnetic stirring bar. The copper salts remaining in the reaction vessel are repeatedly washed with fresh ether until the filtered washings are nearly colorless. Removal of solvent from the filtrate leaves product 2 as a deep red oil (Note 16).

The oil is dissolved in 500 mL of diethyl ether under a nitrogen atmosphere, cooled to -78°C in a dry ice-acetone bath and 18 g (0.11 mol) of tetrafluoroboric acid-diethyl ether complex is added dropwise by syringe over a 30-min period, while the bath temperature is maintained at -78°C . The solution is allowed to warm to room temperature, and the powdery yellow solid is isolated by filtration through a 250-mL, coarse-frit, Schlenk filter tube. The product is washed several times with fresh ether and dried under a stream of nitrogen and then under reduced pressure (oil pump). The yield of salt 3 is 31-39.1 g (60-75%). The product may be used without further purification (Note 17) and may be stored under nitrogen at 0°C for several weeks with no observable decomposition (Note 18).

C. trans-3-Methyl-2-vinylcyclohexanone 4. Compound 3 (31.5 g) and 25 mL of acetonitrile (0.47 mol, 6-fold excess) (Note 19) are placed in a 100-mL round-bottomed flask (Note 20) fitted with a magnetic stirring bar and reflux

condenser. The mixture is heated to reflux for 2 hr under nitrogen, cooled to room temperature and slowly added to 300 mL of diethyl ether. The acetonitrile complex **5** precipitates as a bright yellow solid, and may be removed by suction filtration (Note 21).

The filtrate is washed three times with distilled water to remove excess acetonitrile and then dried over anhydrous magnesium sulfate. Filtration followed by removal of ether leaves the product **4** as a yellow oil (7.1-7.6 g, 64-70%), which may be further purified by short path or bulb-to-bulb distillation (bp 30°C at 0.1 mm) to a colorless liquid (Notes 22, 23).

2. Notes

1. All glassware, syringes and cannulae were routinely flame- or oven-dried and cooled under dry nitrogen.

2. In general, transfers of dry solvent or of solutions are made by 2-mm cannulae inserted through rubber septa capping delivery and receiver vessels. Transfer is made by positive nitrogen pressure applied through a hypodermic needle, while a second needle in the receiver vessel is employed as a vent. Cannulae are available from Hamilton Company, P. O. Box 10030, Reno, NV 89510.

3. Tetrahydrofuran is predried over potassium hydroxide pellets, degassed with nitrogen and freshly distilled under nitrogen from sodium benzophenone ketyl.³

4. Dicarbonyl(cyclopentadienyl)diiron can be readily made on a large scale from iron pentacarbonyl and dicyclopentadiene.⁴ Alternatively it can be purchased from Alfa Products, Morton/Thiokol Inc. or from Strem Chemical Company.

5. Chloroacetaldehyde diethyl acetal was purchased from Aldrich Chemical Company, Inc. This substance is listed as an irritant. Proper care should be exercised when handling it.

6. It is important to stir the product continually to insure effective removal of tetrahydrofuran. If appreciable solvent remains, the vinyl ether complex 1 may not crystallize readily.

7. Ethyl ether was freshly distilled from sodium benzophenone ketyl.

8. Schlenk tubes were purchased from Ace Glass Company, catalogue #7761-36.

9. Filtration is smoothly accomplished by allowing the sodium chloride to settle and filtering the clear supernatant liquor in small portions, transferring the solution to the filtering tube by cannula. If the Celite should become clogged, the surface may be scraped clean, under a strong stream of nitrogen, using a long spatula, in order to increase the filtration rate.

10. Tetrafluoroboric acid - diethyl ether complex was purchased from Columbia Organics Chemical Company, Inc.

11. The salt may be reprecipitated by dissolution in methylene chloride containing a small amount of ethanol, followed by the addition of ether. The product shows the following spectra: IR (CH_2Cl_2) cm^{-1} : 2095, 2045, 1545; NMR (CD_3NO_2) δ : 1.40 (t, 3 H, Me), 2.73 (dd, 1 H, trans-CH=), 3.00 (dd, 1 H, cis-CH=), 4.37 (q, 2 H, OCH_2), 5.50 (c, 5 H, Cp), 7.92 (dd, 1 H, CHOEt). The checkers realized the higher yield only when the preparation was carried out on one-tenth the scale specified here.

12. Cuprous iodide was purchased from Fisher Scientific Company, and purified by recrystallization from saturated aqueous potassium iodide.^{5,6}

13. Methyl lithium was purchased from Aldrich Chemical Company, Inc., and standardized by double titration with benzoic acid in aqueous ethanol and with allyl chloride.⁷

14. 2-Cyclohexen-1-one was purchased from Aldrich Chemical Company, Inc., and purified by vacuum distillation.

15. Alumina was purchased from Woelm and brought to activity IV as directed.

16. As in the preparation of the vinyl ether complex 1, it is very important to remove tetrahydrofuran effectively to promote facile crystallization of product. This is most easily done by removing most of the solvent with a rotary evaporator and then stirring the resulting oil under reduced pressure (oil pump) overnight. Mixing the oil with about 50 mL of ether followed by solvent removal under reduced pressure helped to facilitate removal of traces of tetrahydrofuran. Pure 2 may be obtained as a yellow crystalline solid, which decomposes on heating, by chromatographing the oil on basic alumina (activity IV), eluting with 5% ether in hexane. Compound 2 is characterized by the following spectra: IR(CH₂Cl₂) cm⁻¹: 2000, 1940, 1700; NMR (CDCl₃) δ: 1.17 (t, 6 H, CH₃), 1.43 (d, 2 H, FeCH₂), 1.65 (dd, 1 H, CHCO), 1.70-2.55 (m, 7 H, CH, CH₂), 3.41 (dq, 2 H, OCH₂), 3.76 (dt, 1 H, CHOEt), 4.87 (s, 5 H, Cp).

17. Compound 3 may be recrystallized by dissolution in a minimum volume of nitromethane at 0°C followed by the addition of diethyl ether. The crystalline material decomposes on heating. It is characterized by the following spectra: IR (CH₂CH₂) cm⁻¹: 2090, 2050, 1708; NMR (CD₃NO₂) δ: 1.1 (m, 3 H, CH₃), 1.4-2.6 (m, 8 H, CH, CH₂), 3.28 (d, 1 H, trans-CH₂=), 4.00 (d, 1 H, cis-CH₂=), 5.0 (m, 1 H, CH=), 5.65 (s, 5 H, Cp).

18. However, salt 3 is unstable at room temperature as a solid and in solution and rearranges to the isomeric complex in which the iron center is bound to the carbonyl group of the substituted cyclohexanone.

19. Acetonitrile is freshly distilled under nitrogen from calcium hydride.

20. Because of the ease with which product **4** isomerizes to the conjugated enone in the presence of base, it is imperative that the demetallation and subsequent purification steps be carried out in glassware that is free of basic residues.

21. An inert atmosphere is not necessary.

22. The considerable vapor pressure of **4** causes some loss during vacuum distillation. Although the color of the product is improved by distillation, both IR and NMR spectra of the product before and after distillation show little change.

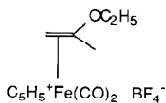
23. Compound **4** is observed to darken on standing in air at room temperature for prolonged periods. Compound **4** is characterized by the following spectra: IR (neat) cm^{-1} : 1708; NMR (CDCl_3) δ : 0.99 (d,d 1 H, CH_3), 1.3-2.8 (m, 8 H, CH, CH_2), 4.98 (dd, 1 H, trans- $\text{CH}_2=$), 5.2 (dd, 1 H, cis- $\text{CH}_2=$), 5.76 (m, 1 H, CH=).

3. Discussion

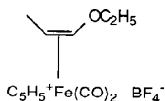
Few reagents are available to the synthetic organic chemist which function as vinyl cation synthons. At present, these include α -phenylseleneoacetaldehyde,⁸ α -silyl aldehydes and ketones,⁹ α,β -epoxysilanes,¹⁰ phenyl vinyl sulfoxide,¹¹ phenyl ethynyl sulfone,^{12,13} phenyl 2-chlorovinyl sulfone,¹³ and activated vinyl halides or ethynyl halides.¹⁵ With the exception of the first two, the use of these reagents is confined to reactions with tertiary enolates or organocuprates.

The procedure given here illustrates the use of readily prepared organoiron complex **1** for the vinylation of a secondary enolate. This salt may be prepared on a large scale from readily available starting materials and can

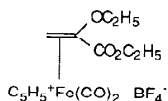
be stored at 0°C without decomposition. The closely related isopropenyl ethyl ether and cis-propenyl ethyl ether-iron complexes, 6 and 7, are similarly prepared from α -bromoacetone^{16,17} and α -bromopropionaldehyde diethyl acetal¹⁸ and have been used as isopropenylating¹⁷ and trans-propenylating¹⁹ reagents with enolates. Complex 8, derived from ethyl 3-bromopyruvate functions as an α -acrylic ester cation with enolates.^{20,21}



6



7



8

Because of their high reactivity, these complex salts react rapidly and regiospecifically, at low temperature, with a number of carbon and heteroatomic nucleophiles, including thiols, amines, and alcohols.²² Finally, exposure of the double bond takes place under particularly mild conditions so that isomerization of the β,γ -unsaturated carbonyl system may be avoided. The present scope of reactions with these vinyl cation synthons is summarized in Table I.

TABLE

VINYLATION OF ENOLATES WITH VINYL CATION EQUIVALENTS

Enolate	Enol Ether Complex	Vinylated Product	Yield %
	1		80
	1		80
	1		80
	1		47 ^a
	7		72
	7		53
	7		91
	6		72
	8		44 ^b 37 ^c
	8		65 ^b
	8		(15) ^d

^aFrom cyclohexenone.^bBy reduction of the initial condensation product with L-selectride.^cBy reduction of the initial condensation product with sodium borohydride.^dBy reduction of the initial condensation product with LiAlH₄ at -78°C.

1. Present address, General Electric Co., Corporate Research and Development, P.O. Box 8, Schenectady, NY 12301.
2. Department of Chemistry, Brandeis University, Waltham, MA 02254.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Dicarbonyl(cyclopentadienyl) (ethyl vinyl ether)iron tetrafluoroborate:
Iron(1+), dicarbonyl(η^5 -2,4-cyclopentadien-1-yl)[(1,2- η)-ethoxyethene]-,
tetrafluoroborate(1-) (10); (75182-42-2)

Dicarbonyl(cyclopentadienyl) iron dimer: Iron, di- μ -carbonyldicarbonyldi- η^5 -
cyclopentadienyldi-, (Fe-Fe) (8); Iron, di- μ -carbonyldicarbonylbis(η^5 -2,4-
cyclopentadien-1-yl)di-, (Fe-Fe) (9); (12154-95-9)

Sodium dicarbonyl(cyclopentadienyl)ferrate: Ferrate (1-), dicarbonyl- π -cyclopentadienyl-, sodium (8); Ferrate (1-), dicarbonyl(η^5 -2,4-cyclopentadien-1-yl)-, sodium (9); (12152-20-4)

Chloroacetaldehyde diethyl acetal: Acetaldehyde, chloro-, diethyl acetal (8);

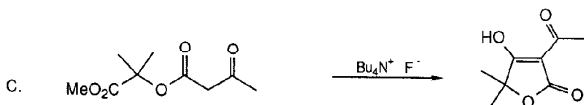
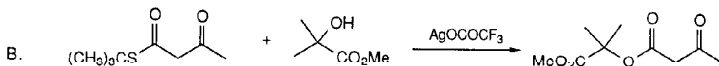
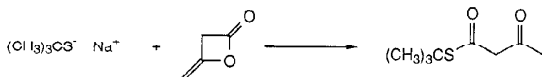
Ethane, 2-chloro-1,1-diethoxy- (9); (621-62-5)

Tetrafluoroboric acid - diethyl ether complex: Borate (1-), tetrafluoro-,

hydrogen, compd. with 1,1'-oxybis[ethane] (1:1) (10); (67969-82-8)

2-Cyclohexen-1-one (8,9); (930-68-7)

PREPARATION OF *tert*-BUTYL ACETOTHIOACETATE AND USE IN THE SYNTHESIS OF
3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(5H)-ONE
*(Acetoacetic acid, 1-thio-, 5-*tert*-butyl ester)*



Submitted by Christina M. J. Fox and Steven V. Ley.¹

Checked by Anura P. Dantanarayana and James D. White.

1. Procedure

Caution! 2-Methylpropane-2-thiol should be handled in an efficient fume hood because of its odor.

A. *S-tert*-Butyl 3-oxobutanthioate. A dry, 2-L, three-necked, round-bottomed flask (Note 1) fitted with a 100-mL pressure-equalizing dropping funnel, thermometer, magnetic stirrer bar and an argon inlet, is charged with

9.8 g (0.24 mol) of sodium hydride as a 60% dispersion in oil (Note 2). The system is flushed with, and kept under, dry argon. The sodium hydride is washed with two 40-mL portions of sodium-dried pentane and the system is purged with dry argon to remove traces of pentane. To the flask is then added 900 mL of dry tetrahydrofuran (Note 3).

The flask is cooled in an ice-salt bath to -5°C and a solution of 20 g (25 mL, 0.22 mol) of 2-methylpropane-2-thiol (Note 2) in 20 mL of dry tetrahydrofuran is added at such a rate as to maintain a steady evolution of hydrogen. The slightly exothermic reaction causes the temperature to rise to 0°C and the colorless solution is stirred at this temperature for 15 min to ensure complete formation of the thiolate. The reaction mixture is then recooled to -5°C and 20.3 g (18.8 mL, 0.24 mol) of diketone (Note 2) is added over 15 min to give a yellow-green solution. The cooling bath is removed and the solution allowed to warm to room temperature.

The reaction is quenched and excess sodium hydride is destroyed by careful addition of 300 mL of saturated ammonium chloride solution. The two-phase mixture is transferred to a 2-L separatory funnel charged with 400 mL of ether. The layers are separated and the organic phase is washed with 300-mL portions of water, saturated sodium bicarbonate solution and brine. The aqueous washes are re-extracted with a 400-mL portion of ether and the combined organic layers are dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator to give the crude product as a deep red oil. Bulb-to-bulb distillation (Note 4) at $95-100^{\circ}\text{C}$ (0.9 mm) gives 22 g (57%) of *S*-pent-butyl 3-oxobutanthioate as a colorless oil (Note 5).

B. *1-Carbomethoxy-1-methylethyl 3-oxobutanoate*. A 500-mL, round-bottomed flask equipped with a magnetic stirrer bar is charged with 10 g (0.085 mol) of methyl 2-hydroxyisobutyrate (Note 2), 17.7 g (0.102 mol) of *S*-tert-butyl 3-oxobutanethioate and 250 mL of dry tetrahydrofuran. The flask is placed in the dark and 22.5 g (0.102 mol) of freshly prepared silver(I) trifluoroacetate (Note 6) is added in two portions. The resulting dark brown suspension is stirred for 15 min (Note 7) and then concentrated to approximately 50 mL with a rotary evaporator. The concentrated mixture is diluted with 200 mL of hexane and the resulting orange-brown precipitate is removed by filtration. The filtered solid is washed with two 50-mL portions of hexane and the combined filtrate and washings concentrated with a rotary evaporator to give an orange-brown oil.

The crude product is chromatographed on 350 g of silica (Note 8) using 1:1 ether-petroleum ether (40-60) as eluant. The chromatography is monitored by TLC (Note 9) and the appropriate fractions are combined. Removal of the solvent with a rotary evaporator gives a pale orange oil (Note 10) which was further purified by distillation to give 11.7 g (68%) of the *O*-ester, bp 69-72°C (0.2 mm) (Note 11).

C. *3-Acetyl-4-hydroxy-5,5-dimethylfuran-2(5H)-one*. A 100-mL, round-bottomed flask equipped with a 50-mL pressure-equalizing dropping funnel and a magnetic stirrer bar is charged with 5 g (0.025 mol) of the acetoacetate and 37 mL (0.037 mol) of tetrabutylammonium fluoride (1 M solution in THF) (Note 2) is added over 5 min. The resulting solution is stirred vigorously for 3 hr (Note 12) and then transferred to a 250-mL separatory funnel containing 50 mL of 6 M hydrochloric acid. The acidified mixture is extracted with three 30-mL portions of ether, each extract being washed with 10 mL of brine. The combined organic extracts are dried over anhydrous sodium sulfate and

concentrated with a rotary evaporator to give 4.3 g of the crude tetronic acid as a yellow solid. Recrystallization from 25 mL of hot 5% ether - petroleum ether gives 1.9 g of the tetronic acid as pale yellow plates, mp 66-67°C (lit²: mp 64-65°C) (Note 13). Concentration of the mother liquor affords a second crop of 0.4 g, mp 63-65°C, giving a combined yield of 54%.

2. Notes

1. The apparatus was oven dried, assembled while hot and cooled under a stream of dry argon.

2. Sodium hydride, 2-methylpropane-2-thiol, diketene, methyl 2-hydroxyisobutyrate and tetrabutylammonium fluoride were purchased from Aldrich Chemical Company, Inc. Diketene was distilled prior to use to remove polymeric species.

3. Tetrahydrofuran was refluxed over and distilled from sodium/benzophenone immediately prior to use.

4. A Kugelrohr apparatus was used for the distillation. The reported temperature is the oven temperature.

5. The checkers found that the yield of this material was substantially higher (83%) when the reaction was conducted at 1/4 scale. Spectral properties of the product³ are as follows: IR (neat) cm^{-1} : 1712, 1676, 1621; ¹H NMR (60 MHz, CDCl_3) δ : 1.5 (s, 9 H, $(\text{CH}_3)_3\text{C}$), 2.3 (s, 3 H, COCH_3), 3.6 (s, 2 H, COCH_2CO), 5.3 (s, $\text{COCH}=\text{C}(\text{OH})$).

6. Silver(I) trifluoroacetate may be obtained commercially but it is recommended that it be freshly prepared.⁴ Trifluoroacetic acid (18 mL, 0.24 mol) is added to silver(I) oxide (0.12 mol), freshly precipitated from silver nitrate (20 g, 0.12 mol) and sodium hydroxide (4.7 g, 0.12 mol) in water (30

mL). The solution is filtered and evaporated to dryness under reduced pressure. The crude product is purified by dissolving it in ether (150 mL), filtering through decolorizing charcoal and evaporation to give the product as a white crystalline solid (19.3 g, 74%).

7. The time reported represents the average reaction time. The reaction can be followed by TLC, visualizing with iodine and 10% phosphomolybdic acid in ethanol followed by heating on a hot plate.

8. Merck Kieselgel 60 silica gel (230-400 mesh) was used.

9. Merck precoated silica gel 60 F-254 plates were used, visualizing with iodine.

10. In some cases, the product is contaminated with a yellow solid even after chromatography. This is removed prior to distillation by filtering through a short pad of Celite.

11. The spectral properties of the product² are as follows: IR (neat) cm^{-1} : 1745, 1720; ^1H NMR δ (90 MHz, CDCl_3): 1.57 (s, 6 H, $(\text{CH}_3)_2\text{C}$), 2.28 (s, 3 H, COCH_3), 3.44 (s, 2 H, COCH_2CO), 3.72 (s, 3 H, CO_2CH_3).

12. The reaction is monitored by TLC and quenched when starting material has been consumed.

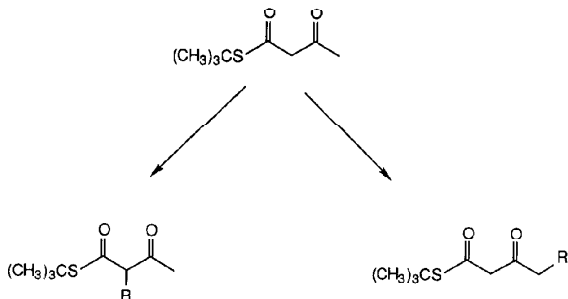
13. Spectral properties of the product² are as follows: IR (KBr) cm^{-1} : 1758, 1685, 1610; ^1H NMR (60 MHz, CDCl_3) δ : 1.50 and 1.51 (2 s, 6 H, $\text{C}(\text{CH}_3)_2$), 2.5 (s, 3 H, COCH_3), 9.25 (br s, 1 H, OH).

3. Discussion

Selective alkylation of β -keto esters via either anions or dianions is an important synthetic transformation.⁵ Equally, thioesters may be transesterified in the presence of thiophilic metal cations.⁶ These two features

can be usefully combined in one substrate, tert-butyl acetothioacetate, the subject of this *Organic Syntheses* procedure.

Alkylation at the 2-position can be achieved by formation of the anion with sodium hydride in 1,2-dimethoxyethane (DME) at 0°C followed by reaction with an alkyl halide at room temperature. Alternatively, selective alkylation at C-4 involves sequential treatment with sodium hydride (at -10°C) and butyllithium in DME (at -40°C) to form the dianion, followed by kinetic alkylation with an alkyl halide (or carbonyl compound).⁷



The choice of DME as solvent in these reactions is important as other solvents are much less successful and lead to unwanted side products.

Transesterification of the resulting alkylated β -keto thioesters to the corresponding oxo esters is readily achieved using alcohols under various metal catalysis.⁶

The alcohols used may also contain fairly sensitive functional groups, e.g., esters, halides, silyl ethers, etc. In this work, therefore, tert-butyl acetothioacetate is behaving as a synthetic equivalent to diketene. When this methodology is used, it is possible to devise very short syntheses of acyl telonic acids⁷ and novel macrocyclic structures.⁸

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

tert-Butyl acetothioacetate: Acetoacetic acid, 1-thio-, S-tert-butyl ester (8,9); (15925-47-0)

2-Methylpropane-2-thiol: 2-Propanethiol, 2-methyl- (8,9); (75-66-1)

Sodium hydride (8,9): (7646-69-7)

Diketene: 2-Oxetanone, 4-methylene- (8,9); (674-82-8)

Methyl 2-hydroxyisobutyrate: Lactic acid, 2-methyl-, methyl ester (8);

Propanoic acid, 2-hydroxy-2-methyl-, methyl ester (9): (2110-78-3)

Silver(I) trifluoroacetate: Acetic acid, trifluoro-, silver (1 + salt)
(8,9); (2966-50-9)

Tetrabutylammonium fluoride: Ammonium, tetrabutyl-, fluoride (8);

1-Butanaminium, N,N,N-tributyl-, fluoride (9); (429-41-4)

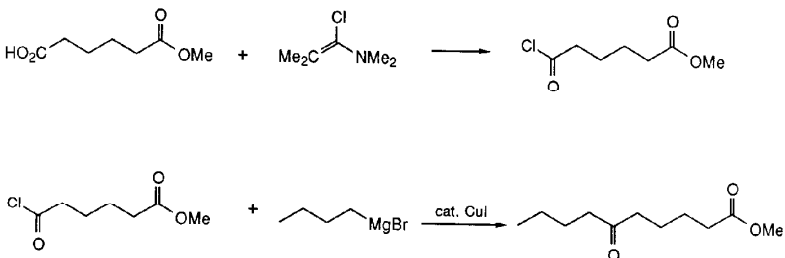
Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

Silver(I) oxide: Silver oxide (8); Silver oxide (Ag_2O) (9); (20667-12-3)

KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS:

METHYL 6-OXODECANOATE

(Decanoic acid, 6-oxo-, methyl ester)



Submitted by Tamotsu Fujisawa and Toshio Sato.¹

Checked by Cynthia Smith and Andrew S. Kende.

1. Procedure

A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, an addition funnel for solids (Note 1), and a rubber septum is flushed with nitrogen. The flask is charged with 50 mL of dichloromethane (Note 2) and 6.92 g (0.052 mol) of 1-chloro-N,N,2-trimethylpropenylamine (Note 3). The solution is stirred and cooled in an ice bath and 8.01 g (0.050 mol) of adipic acid monomethyl ester (Note 4) is added slowly by means of a syringe over 10 min. After the addition is complete, the cooling bath is removed and the contents of the flask are stirred for 30 min at room temperature (Note 5). The flask is cooled in an ice-salt bath to -15°C. Then 100 mL of tetrahydrofuran (Note 6) and 0.48 g (0.0025 mol) of copper(I) iodide (Note 7) are added to the flask through the septum and the funnel,

respectively. To this stirred mixture is added 50.5 mL (0.052 mol) of a 1.03 M solution of butylmagnesium bromide (Note 8) in tetrahydrofuran over 1 hr using a syringe pump, while the internal temperature is maintained below -10°C . The reaction mixture is stirred for an additional hour at -15°C . After 100 mL of 2 M hydrochloric acid solution has been poured into the flask in one portion, the mixture is transferred to a separatory funnel and the organic layer is separated. The aqueous layer is extracted with two 100-mL portions of hexane. The combined organic extracts are washed with five 100-mL portions of 2 M hydrochloric acid solution (Note 9), 100 mL of 5% sodium thiosulfate solution, two 100-mL portions of saturated sodium bicarbonate solution, and 100 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under reduced pressure and the residual liquid is distilled with a short-necked Claisen distillation flask. After separation of a small forerun (<0.3 g) (Note 10), 8.53-8.67 g (85-86%) of methyl 6-oxodecanoate is collected, bp $106-110^{\circ}\text{C}$ (2.8 mm) (Note 11).

2. Notes

1. A simple bent glass tube is useful as an addition funnel for copper(I) iodide.

2. Dichloromethane was distilled over calcium hydride, and stored over molecular sieves 4 Å.

3. N,N-Dimethylisobutyramide (Gavrilov, N.; Koperina, A.; Klutcharova, M. *Bull. Soc. Chim. France* **1945**, 12, 773) was converted to 1-chloro-N,N,2-trimethylpropenylamine according to the procedure of *Org. Synth.* **1979**, 59, 26, in 61% yield, bp $118-121^{\circ}\text{C}$. Freshly-distilled oxalyl chloride was used instead of phosgene. The propenylamine should be handled carefully in a syringe to avoid its rapid hydrolysis by moisture.

4. Adipic acid monomethyl ester was purchased from Nakarai Chemicals, or Aldrich Chemical Company, Inc. and distilled before use, bp 155-158°C (7 mm).
5. In a separate experiment, formation of adipic acid monomethyl ester monochloride was observed.²
6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
7. Copper(I) iodide purchased from Wako Chemicals was used without purification.
8. Butylmagnesium bromide was prepared from magnesium and butyl bromide in tetrahydrofuran at room temperature by a standard procedure (*Org. Synth.* 1978, 58, 127), and titrated by the procedure of Eastham, et al.³
9. The organic extracts must be washed four or five times to remove N,N-dimethylisobutyramide.
10. The forerun consisted of N,N-dimethylisobutyramide, other by-products, and methyl 6-oxodecanoate.
11. The reported physical constants are bp 149°C (13.5 mm),⁴ 97-103°C (3.5 mm),⁵ n_D^{20} 1.4377,⁴ n_D^{25} 1.4376.⁵ Gas chromatographic analysis of the product using a 3 mm x 1-m stainless steel column, 15% SE-30 on 60-80 mesh chromosorb W (AW), 150°C, 50 mL of nitrogen per min indicated a purity of 99.6% (the retention time is 6.9 min). The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 2960, 2870, 1740, 1714, 1454, 1435, 1415, 1370, 1200, and 1175; ^1H NMR (60 MHz, CCl_4) δ : 0.9 (t, 3 H, J = 7, CH_3), 1.06-1.86 (m, 8 H, CH_2), 2.06-2.56 (m, 6 H, $\text{CH}_2\text{C=O}$), 3.60 (s, 3 H, OCH_3).

3. Discussion

The direct coupling of Grignard reagents with carboxylic acids is not generally useful for ketone synthesis because of the accompanying formation of tertiary alcohols. An exception is the recently-published method using a nickel catalyst.⁶ In order to accomplish such a chemoselective ketone synthesis, the method of activation of carboxylic acid in situ is important, and several activating reagents have been proposed for the purpose, such as a bulky acyl chloride,⁷ dichlorotriphenylphosphorane,⁸ or N,N-diphenyl-p-methoxyphenylchloromethylenammonium chloride,⁹ which react with carboxylic acids to produce mixed anhydrides, carboxyphosphonium salts, or carboxymethylenammonium salts, respectively.

The present procedure, reported earlier by the submitters,¹⁰ illustrates a general method for ketone synthesis in a one-pot operation using an α -chloroamine as a condensation reagent. 1-Chloro-N,N,2-trimethylpropenylamine reacts with carboxylic acids to produce the corresponding acyl chlorides² which instantaneously couple with Grignard reagents in the presence of a copper catalyst to give ketones. The utility of the procedure is as follows: (1) an equimolecular amount of Grignard reagent is sufficient to complete the reaction of carboxylic acid; and (2) the exceptionally high chemoselectivity of the reaction tolerates various kinds of functional groups such as nitrile, halide, ester and even ketone.¹⁰

1. Chemistry Department of Resources, Mie University, Tsu Mie 514, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

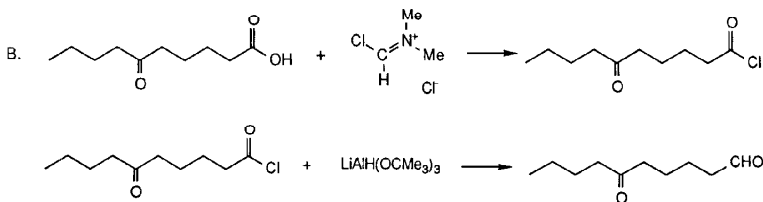
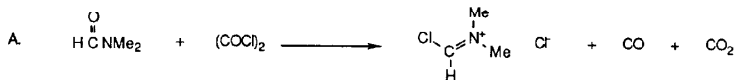
Methyl 6-oxodecanoate: Decanoic acid, 6-oxo-, methyl ester (10); (61820-00-6)

1-Chloro-N,N,2-trimethylpropenylamine: Propenylamine, 1-chloro-N,N,2-trimethyl- (8); 1-Propen-1-amine, 1-chloro-N,N,2-trimethyl- (9); (26189-59-3)

Adipic acid monomethyl ester (8); Hexanedioic acid, monomethyl ester (9); (627-91-8)

REDUCTION OF CARBOXYLIC ACIDS TO ALDEHYDES: 6-OXODECANAL

(Decanal, 6-oxo-)



Submitted by Tamotsu Fujisawa and Toshio Sato.¹

Checked by Cynthia Smith and Andrew S. Kende.

1. Procedure

Caution! Oxalyl chloride is toxic. This preparation should be carried out in a well-ventilated hood.

A. *N,N*-Dimethylchloromethylenammonium chloride. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer (Note 1), and a three way stopcock fitted with a drying tube containing anhydrous calcium chloride and a rubber septum. The flask is charged with 50 mL of dichloromethane (Note 2) and 3.0/ g (0.042 mol) of *N,N*-dimethylformamide (Note 3) added through the septum from a syringe, and cooled in an ice bath. To the cooled mixture is slowly added 5.23 mL (0.06 mol) of oxalyl chloride (Note 4) by means of a syringe. The addition is accompanied by gas evolution and formation of a white precipitate. The reaction mixture is stirred for an

additional hour at 0°C. Excess oxalyl chloride and solvent are removed under reduced pressure by first using a water aspirator and then a rotary pump at room temperature through the drying tube. The white solid remaining in the flask is N,N-dimethylchloromethylenammonium chloride, which is used directly in Part B.

D. *6-Oxodecanal*. The drying tube is removed and the flask is flushed with nitrogen. A nitrogen atmosphere is maintained throughout the subsequent reaction. A dropping funnel is attached and charged with 7.45 g (0.04 mol) of 6-oxodecanoic acid (Note 5), 3.32 g of pyridine (Note 6) and 80 mL of tetrahydrofuran (Note 7), which are mixed well by shaking. The flask is charged with 45 mL of acetonitrile (Note 8) and 80 mL of tetrahydrofuran, and cooled (methanol-liquid nitrogen) to -30°C. The contents of the funnel are added to the flask at -30°C over 30 min. The reaction mixture is stirred at -30°C for an additional hour and at -20°C for 30 min. After the mixture is cooled to -90°C (Note 9), 34 mL (0.046 mol) of a 1.35 M solution of lithium tri(tert-butoxy)aluminum hydride in tetrahydrofuran (Note 10) is injected through the septum by means of a syringe over 30 min, while the internal temperature is kept below -85°C. Stirring is continued for an additional 30 min at -90°C. To the flask is added 50 mL of 2 M hydrochloric acid solution, and the cooling bath is immediately removed. The organic layer is separated and the aqueous layer is extracted with three 50-mL portions of ether. The combined organic extracts are washed with two 50-mL portions of saturated sodium hydrogen carbonate solution and 50 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed with a rotary evaporator and the residual liquid is distilled under reduced pressure to yield 5.78-6.35 g (85-93%) of 6-oxodecanal as a fragrant liquid, bp 85-90°C (1.4 mm) (Note 11).

2. Notes

1. The thermometer must be able to measure temperatures as low as -90°C .
2. Dichloromethane was distilled from calcium hydride, and stored over molecular sieves 4 \AA .
3. N,N-Dimethylformamide was distilled under reduced pressure, bp $45-47^{\circ}\text{C}$ (20 mm), and stored over molecular sieves 4 \AA .
4. Oxalyl chloride purchased from Wako Chemicals was used without purification. The checkers found that oxalyl chloride, purchased from Aldrich Chemical Company, Inc., gives better yields if freshly distilled.
5. 6-Oxodecanoic acid was obtained by hydrolysis of methyl 6-oxodecanoate prepared by the method of *Org. Synth.*² as follows: Twenty grams (0.100 mol) of methyl 6-oxodecanoate was treated with 200 mL of 1 M potassium hydroxide solution at room temperature overnight. The alkaline solution was washed with two 50-mL portions of ether, and acidified with 50 mL of 6 M hydrochloric acid solution at 0°C . The acidic layer was extracted with three 100-mL portions of ether. The ethereal extracts were dried over sodium sulfate, and filtered. Removal of the solvent under reduced pressure and recrystallization of the residual white solid from hexane gave 17.85 g (96%) of 6-oxodecanoic acid, mp $45.0-45.5^{\circ}\text{C}$ (lit.³ mp $45-46^{\circ}\text{C}$).
6. Pyridine was distilled from calcium hydride, and stored over molecular sieves 4 \AA .
7. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
8. Acetonitrile was distilled from calcium hydride, and stored over molecular sieves 4 \AA .
9. The checkers used a 1:1 methanol:ethanol/liquid nitrogen bath.

additional hour at 0°C. Excess oxalyl chloride and solvent are removed under reduced pressure by first using a water aspirator and then a rotary pump at room temperature through the drying tube. The white solid remaining in the flask is N,N-dimethylchloromethylenammonium chloride, which is used directly in Part B.

B. 6-Oxodecanal. The drying tube is removed and the flask is flushed with nitrogen. A nitrogen atmosphere is maintained throughout the subsequent reaction. A dropping funnel is attached and charged with 7.45 g (0.04 mol) of 6-oxodecanoic acid (Note 5), 3.32 g of pyridine (Note 6) and 80 mL of tetrahydrofuran (Note 7), which are mixed well by shaking. The flask is charged with 45 mL of acetonitrile (Note 8) and 80 mL of tetrahydrofuran, and cooled (methanol-liquid nitrogen) to -30°C. The contents of the funnel are added to the flask at -30°C over 30 min. The reaction mixture is stirred at -30°C for an additional hour and at -20°C for 30 min. After the mixture is cooled to -90°C (Note 9), 34 mL (0.046 mol) of a 1.35 M solution of lithium tri(tert-butoxy)aluminum hydride in tetrahydrofuran (Note 10) is injected through the septum by means of a syringe over 30 min, while the internal temperature is kept below -85°C. Stirring is continued for an additional 30 min at -90°C. To the flask is added 50 mL of 2 M hydrochloric acid solution, and the cooling bath is immediately removed. The organic layer is separated and the aqueous layer is extracted with three 50-mL portions of ether. The combined organic extracts are washed with two 50-mL portions of saturated sodium hydrogen carbonate solution and 50 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed with a rotary evaporator and the residual liquid is distilled under reduced pressure to yield 5.78-6.35 g (85-93%) of 6-oxodecanal as a fragrant liquid, bp 85-90°C (1.4 mm) (Note 11).

2. Notes

1. The thermometer must be able to measure temperatures as low as -90°C .
2. Dichloromethane was distilled from calcium hydride, and stored over molecular sieves 4 Å.
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4. Oxalyl chloride purchased from Wako Chemicals was used without purification. The checkers found that oxalyl chloride, purchased from Aldrich Chemical Company, Inc., gives better yields if freshly distilled.
5. 6 Oxodecanoic acid was obtained by hydrolysis of methyl 6-oxodecanoate prepared by the method of *Org. Synth.*² as follows: Twenty grams (0.100 mol) of methyl 6-oxodecanoate was treated with 200 mL of 1 M potassium hydroxide solution at room temperature overnight. The alkaline solution was washed with two 50-mL portions of ether, and acidified with 50 mL of 6 M hydrochloric acid solution at 0°C . The acidic layer was extracted with three 100-mL portions of ether. The ethereal extracts were dried over sodium sulfate, and filtered. Removal of the solvent under reduced pressure and recrystallization of the residual white solid from hexane gave 17.85 g (96%) of 6-oxodecanoic acid, mp $45.0-45.5^{\circ}\text{C}$ (lit.³ mp $45-46^{\circ}\text{C}$).
6. Pyridine was distilled from calcium hydride, and stored over molecular sieves 4 Å.
7. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
8. Acetonitrile was distilled from calcium hydride, and stored over molecular sieves 4 Å.
9. The checkers used a 1:1 methanol:ethanol/liquid nitrogen bath.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

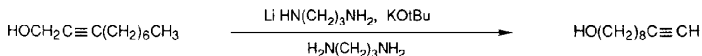
6-Oxodecanal: Decanal, 6-oxo- (10); (63049-53-6)

6-Oxodecanoic acid: Decanoic acid, 6-oxo- (9); (4144-60-9)

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)

N,N-Dimethylchloromethylenammonium chloride: Ammonium,
(chloromethylene)dimethyl-, chloride (8); Methanaminium, N-(chloromethylene)-
N-methyl, chloride (9); (3724-43-4)

TRIPLE BOND ISOMERIZATIONS: 2- TO 9-DECYN-1-OL



Submitted by Suzanne R. Abrams and Angela C. Shaw.¹

Checked by Maurizio Taddei and Ian Fleming.

1. Procedure

Caution: This preparation should be carried out in an efficient hood and the operator should wear gloves to protect against spillage of corrosive 1,3-diaminopropane.

A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel to which an argon inlet is attached, and a condenser fitted with a drying tube filled with potassium hydroxide pellets (Note 1). The flask is charged with lithium (4.2 g, 0.6 mol, Note 2) and 1,3-diaminopropane (300 mL, Note 3). The mixture is stirred at room temperature for 30 min. A slight exothermic reaction takes place as the lithium dissolves.

The mixture is stirred and heated in an oil bath at 70°C until the blue color discharges (approximately 3 hr), affording a white suspension of the lithium amide. The reaction mixture is cooled to room temperature, and potassium tert-butoxide (44 g, 0.4 mol, Note 4) is added to the flask using a powder funnel. The resultant pale yellow solution is stirred for 20 min at room temperature, and then 2-decyn-1-ol (15.4 g, 0.1 mol, Note 5) is added over 10 min by means of the dropping funnel (Note 6). Residual 2-decyn-1-ol

is washed into the flask with 1,3-diaminopropane (20 mL). The reddish brown mixture is stirred for 30 min and then poured into 1 L of ice water and extracted four times with 500-mL portions of hexane. The hexane extracts are combined and washed successively with 1 L each of water, 10% hydrochloric acid, and saturated sodium chloride solution. The hexane solution is dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator. The crude product is distilled under reduced pressure to give 9-decyn-1-ol (12.8-13.5 g, 83-88%) (Notes 7, 8), as a colorless oil, bp 86-88°C/0.5 mm.

2. Notes

1. All glassware should be previously dried in an oven at 110°C for at least 2 hr.

2. Lithium wire (3.2 mm dia., 0.02% Na, Alfa Products, Morton/Thiokol Inc.) is cut into 1-cm pieces, then washed with hexane and quickly weighed into a tared beaker of hexane. The checkers also used lithium shot (BDH); the lithium did not all dissolve at room temperature, and heating at 70°C for 6 hr was necessary to discharge the blue color.

3. 1,3-Diaminopropane (97%, Aldrich Chemical Company, Inc.) was distilled at atmospheric pressure under nitrogen from barium oxide and stored over molecular sieves (4 Å).

4. Potassium tert-butoxide (Aldrich Chemical Company, Inc.) was used without further purification, and was added over 1-2 min.

5. 2-Decyn-1-ol (Farchan Labs., Lancaster Synthesis) was used without further purification. Upon addition of 2-decyn-1-ol to the reaction mixture slight warming is observed. The temperature is maintained at 25-30°C using a water bath.

6. The checkers used a syringe, injecting through a rubber septum.

7. The submitters used a Kugelrohr apparatus with an oven temperature of 80-90°C/0.05 mm.

8. The isomeric purity of the product is greater than 99% as determined by GLC of the trimethylsilyl ether. 9-Decyn-1-ol (n_D^{26} 1.4552) has the following spectroscopic characteristics: ^1H NMR (CDCl_3) δ : 1.1-1.7 (m, 12 H), 1.9 (t, $J = 1.5$, $\text{C}\equiv\text{CH}$), 2.1 (m, 2 H, $\text{CH}_2\text{C}\equiv\text{C}$), 3.6 (t, 2 H, $J = 6$, OCH_2); IR (film) ν_{max} cm^{-1} : 3400 (br), 3300 (s), 2100 (w), 1050 (s).

3. Discussion

In 1975 Brown and Yamashita² reported that a triple bond in any position of a straight chain hydrocarbon or acetylenic alcohol, when treated with a sufficiently strong base, could be isomerized exclusively to the free terminus of the chain. The "zipper reaction" thus provides a general solution to the problem of remote functionalization of a long hydrocarbon chain. Isomerizations along chains of thirty carbon atoms have been achieved. Isomerization is blocked by alkyl or hydroxyl branches; the triple bond then migrates to the free terminus.

The base employed by Brown and Yamashita was the potassium salt of 1,3-diaminopropane, prepared by reaction of potassium hydride with the solvent of the reaction, 1,3-diaminopropane. The reagent is very effective, and yields of isomerically pure products are high, but potassium hydride is hazardous, expensive and difficult to handle.

We and others have developed alternative methods for preparing the isomerization reagent.³⁻⁶ Hommes and Brandsma³ first made potassium or sodium amide in liquid ammonia and then replaced the solvent with 1,3-diaminopropane.

Kimmel and Becker⁴ treated molten potassium or sodium with 1,3-diaminopropane in a flask immersed in an ultrasonic bath at 90°C. We^{5,6} found that sodium hydride reacts with 1,3-diaminopropane, or 1,2-diaminoethane, on warming. All of these methods produce effective isomerization reagents with comparable conversions and yields. The lithium salt alone is a poor isomerization reagent; however, addition of potassium tert-butoxide affords a reagent which very effectively isomerizes triple bonds. This procedure, presented here, is our most refined method.⁷ It is straightforward, gives reproducibly high yields, employs inexpensive reagents, and can be safely carried out on a large scale.

It is not satisfactory to employ 1,2-diaminoethane in place of 1,3-diaminopropane. The reagent is not as stable; addition of potassium tert-butoxide results in the immediate formation of a deep purple solution. Isomerizations proceed to completion, but yields are somewhat reduced (by about 10% in the case of the rearrangement of 2- to 9-decyn-1-ol).

1. Plant Biotechnology Institute, National Research Council of Canada, 110 Gymnasium Road, Saskatoon, Saskatchewan, S7N 0W9, Canada.
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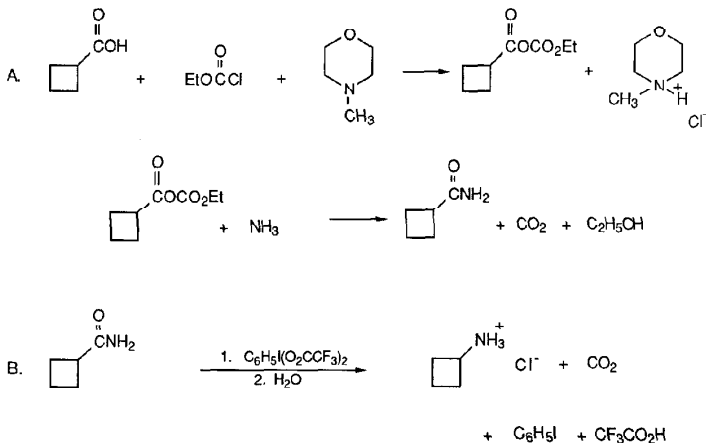
Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

2-Decyn-1-ol (8,9); (4117-14-0)

9-Decyn-1-ol (8,9), (17643-36-6)

1,3-Diaminopropane: 1,3-Propanediamine (8,9); (109-76-2)

**HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS USING
[I,I-BIS(TRIFLUOROACETOXY)]IODOBENZENE: CYCLOBUTYLAMINE HYDROCHLORIDE
FROM CYCLOBUTANECARBOXAMIDE
(Cyclobutanamine hydrochloride)**



Submitted by Merrick R. Almond, Julie B. Stimmel, E. Alan Thompson,
and G. Marc Loudon.¹

Checked by C. Eric Schwartz and Edwin Vedejs.

1. Procedure

A. *Cyclobutanecarboxamide* (Note 1). A 250-mL, round-bottomed flask, equipped with a mechanical stirrer and a drying tube (Drierite), is flame-dried and allowed to cool to room temperature. The flask is equipped with a

punctured rubber septum, through which is inserted a -90°C thermometer. The flask is subjected to a nitrogen atmosphere by inserting a syringe needle connected to a nitrogen bubbler through the septum along with a second syringe needle used as an outlet. Under a flow of nitrogen the flask is charged via syringe with cyclobutanecarboxylic acid (6.0 g, 59.9 mmol, Note 2), 60 mL of dry tetrahydrofuran (Note 2), and N-methylmorpholine (6.6 mL, 59.9 mmol, Note 2). Stirring is commenced, and the solution is cooled to an internal temperature of -15°C using a dry ice-isopropyl alcohol bath at -20° to -25°C . Ethyl chloroformate (5.7 mL, 59.9 mmol, Notes 2, 3) is added and the solution is stirred for 5 min. The addition of ethyl chloroformate results in an internal temperature rise to $+8^{\circ}$ to $+10^{\circ}\text{C}$ and the precipitation of a white solid. Following the precipitation the continuously stirred mixture, still in the dry ice-isopropyl alcohol bath, is allowed to reach an internal temperature of -14°C . Anhydrous ammonia (Note 2), introduced into the flask via a syringe needle, is vigorously bubbled through the solution for 10 min with manual stirring; the internal temperature rises abruptly to 25°C . With the flask still in the cooling bath, stirring is continued for an additional 30 min, and the reaction mixture is stored in the freezer at -15°C overnight (Note 4).

The slurry is stirred with tetrahydrofuran (100 mL) at room temperature for 5 min and ammonium salts are removed by suction filtration through a Buchner funnel. After the solids are rinsed with tetrahydrofuran (20 mL), the filtrate is passed through a plug of silica gel (65 g Merck 60 230-400 mesh) in a coarse porosity sintered-glass filter funnel with aspirator suction. The funnel is further washed with acetonitrile (750 mL) and the combined filtrates are evaporated (rotary evaporator) to give a white solid. This material is recrystallized by heating (steam bath) with 8:1 ether:ethanol (70 mL); if

necessary, ethanol is added dropwise to obtain a homogeneous solution. Cooling to room temperature results in white flakes which are collected by filtration (ether wash), 2.93 g. Two more crops (1.3 g total) are obtained by repeating the process for a total of 4.23 g (71%), mp 152-153°C (lit.² 155°C). In several similar runs, the yield of amide was 4.23-4.49 g (71-76%).

D. *Cyclobutylamine hydrochloride*. A 500-mL, round-bottomed flask is equipped with a magnetic stirring bar and covered with aluminum foil. To the flask is added a solution of [I,I-bis(trifluoroacetoxy)iodo]benzene (16.13 g, 37.5 mmol; Note 5) in 37.5 mL of acetonitrile, and the resulting solution is diluted with 37.5 mL of distilled deionized water. Cyclobutanecarboxamide (2.48 g, 25 mmol) is added; the amide quickly dissolves. Stirring is continued for 4 hr. and the acetonitrile is removed with a rotary evaporator. The aqueous layer is stirred with 250 mL of diethyl ether; to the stirring mixture is added 50 mL of concd hydrochloric acid (Note 6). The mixture is transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with two 125-mL portions of ether. The organic fractions are combined and extracted with 75 mL of 2N hydrochloric acid. The aqueous fractions are combined and concentrated with a rotary evaporator using a vacuum pump. Benzene (50 mL, Note 2) is added to the residue and the solution is concentrated with the rotary evaporator, again using a vacuum pump. Addition of benzene and concentration is repeated five more times. The crude solid is dried under reduced pressure over sulfuric acid overnight. To the product is added 5 mL of absolute ethanol and 35 mL of anhydrous ether, and the solution is heated at reflux on a steam bath. Ethanol is added slowly to the mixture, with swirling, until all the material is dissolved; the solution is cooled to room temperature. Anhydrous ether is added slowly until crystallization just begins. The flask is placed in the freezer and the

product is allowed to crystallize. Filtration of the product and drying overnight under reduced pressure over phosphorus pentoxide yields 1.86-2.06 g of cyclobutylamine hydrochloride (69-77%), mp 183-185°C (lit.³ 183-184°C).

2. Notes

1. The method used here for preparing the amide gives superior yields to two literature methods that employ the acid chloride as an intermediate.³

2. Sources and purification of reagents are as follows: Cyclobutanecarboxylic acid, 98%, is from Aldrich Chemical Company, Inc., and is vacuum distilled before use. Tetrahydrofuran is freshly distilled from sodium-benzophenone under nitrogen. N-Methylmorpholine, 99%, is from Aldrich Chemical Company, Inc., and is pre-dried over barium oxide, distilled from ninhydrin, and stored over sodium hydroxide pellets. Ethyl chloroformate, 97%, is from Aldrich Chemical Company, Inc., and is freshly distilled prior to use under a nitrogen atmosphere. Anhydrous ammonia (99.99% min) is from a Matheson lecture bottle. The silica gel used for flash chromatography is Davidson grade 62, 60-200 mesh. Acetonitrile is from Fisher Scientific Company, HPLC grade. Benzene, spectral grade, is from J. T. Baker.

3. The submitters have repeated this preparation with isobutyl chloroformate substituted for ethyl chloroformate with no increase in yield.

4. The submitters purified the product by flash chromatography as follows. Tetrahydrofuran is removed on a rotary evaporator. Silica gel (20 g) and 80 mL of acetonitrile (Note 2) are added to the flask. The resulting slurry is concentrated with a rotary evaporator to a dry solid. The material is scraped from the flask and loaded onto a flash chromatography column (50 mm

diameter) containing 250 g of silica gel, prepared according to the method of Still.⁴ The column is eluted with acetonitrile (Note 2) at a flow rate of 0.5 in/min (Note 7). The first 500 mL of eluent is measured with a graduated cylinder and discarded, and then fractions (80 x 23 mL) are collected in test tubes. A small aliquot (5 μ L) is taken from every other tube and these aliquots are spotted in successive lanes on a silica gel thin-layer chromatography plate (E. Merck No. 5735), which is developed with acetonitrile. The plate is dried and the product detected by the chlorine/starch-potassium iodide procedure (Note 8). This thin-layer analysis reveals that early fractions from the flash chromatography column contain a small amount of ethyl carbamate impurity at R_f = 0.53; another unidentified impurity (R_f = 0.37) follows. The product cyclobutanecarboxamide emerges next, beginning at about fraction 14 (R_f = 0.26). The product appears as a blue-black spot on a faint blue background. There is some overlap between the second impurity and the product. The fractions containing only product are pooled and concentrated in a 1-L, round-bottomed flask with a rotary evaporator to a white crystalline solid. This product is dried under reduced pressure overnight to yield cyclobutanecarboxamide (4.52 g, 76.1%), mp 156-157.5°C (lit.² 155°C).

5. [I,I-Bis(trifluoroacetoxy)iodo]benzene is prepared by dissolving, with heating, a given number of grams of (I,I-diacetoxyiodo)benzene (iodobenzene diacetate, Aldrich Chemical Company, Inc.; see also *Org. Synth., Collect. Vol. V*, 1973, 660) in twice that number of milliliters of trifluoroacetic acid that has been distilled from a small amount of phosphorus pentoxide. For example, 40 g of (I,I,-diacetoxyiodo)benzene is dissolved in 80 mL of trifluoroacetic acid in an Erlenmeyer flask, which is allowed to stand in a dark drawer. The [I,I-bis(trifluoroacetoxy)iodo]benzene

crystallizes and is isolated by suction filtration within 2 hr (53-70% yield). If crystallization does not occur it can be induced by scratching or seeding. It has been the submitters' experience that if a dark yellow trifluoroacetic acid supernatant is obtained, the yield of the rearrangement reaction carried out with the resulting reagent is invariably poor; the supernatant solution is normally very lightly colored. If the proportion of trifluoroacetic acid is reduced, a greater weight of crystals is obtained; however, this material gives considerably lower yields in the rearrangement. Upon standing, particularly in the light, [I,I-bis(trifluoroacetoxy)-iodo]benzene turns yellow; this reagent also gives poor yields in the rearrangement and yellow reaction mixtures; the reaction mixtures of satisfactory rearrangements are water-white. The reagent should be stored in a dark bottle under nitrogen or argon.

The submitters have also found that the rearrangement can be effected with (I,I diacetoxiodo)benzene or iodosobenzene and two equivalents of trifluoroacetic acid.

6. Hydrochloric acid not only provides the chloride counter-ion for the final product, but also effects the removal of any unreacted (I,I-bis(trifluoroacetoxy)iodo]benzene as the ether-soluble (I,I-dichloriodo)benzene (iodobenzene dichloride).

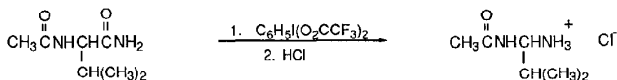
7. A nitrogen regulator has to be set at 8 p.s.i. to achieve a pressure sufficient to maintain a flow rate of 0.5 in/min. A slower flow rate results in poor resolution.

8. The thin-layer plate is chlorinated for 1 min by placing it in a chamber with potassium chlorate to which a few drops of hydrochloric acid are added. The plate is dried in air for 10 min and then sprayed with aqueous 1% starch-1% potassium iodide solution.

3. Discussion

Hypervalent iodine reagents have been used recently for a variety of organic transformations,⁵ including α -hydroxylation of ketones.⁶ (I,I-Dicarboxyiodo)benzene derivatives have also found a variety of uses.⁷ The use of (I,I-diacetoxyiodo)benzene for the conversion of amides to carbamates in alcohol solvents was studied by Smith and Baumgarten,⁸ and the "acidic Hofmann rearrangement" utilized in this preparation, in which amides are converted directly into the corresponding amines in partially aqueous solution, was developed by Loudon, et al.⁹ and applied to a variety of amides; the mechanism of the rearrangement has also been studied.¹⁰ The rearrangement occurs with retention of stereochemical configuration at the migrating alkyl group,^{8,9b,11} and the relative rates of rearrangement generally follow the migratory preferences observed in the Lossen rearrangement, Baeyer-Villiger reaction, and similar migrations to electron-deficient centers.

A particularly interesting application of this reagent is the preparation of "geminal amino amides," a novel class of compounds that have surprising stability in aqueous solution.¹² These derivatives have found application in



the construction of retro-inverso-peptides,¹³ in the design of a novel class of prodrugs,¹⁴ and as intermediates in a carboxyl-terminal peptide degradation.¹⁵

One important restriction is that the reaction cannot be applied to amides in which the carboxamide group is directly attached to an aromatic ring; in these cases, rearrangement occurs, but the resulting aromatic amine is more rapidly oxidized than the starting amide by remaining reagent.¹⁶

Although iodine(III) reagents attack double bonds, the rearrangement of the amide group is, at least in some cases, more rapid than electrophilic attack on alkenes. Thus 3-cyclohexene-1-carboxamide rearranges smoothly to the corresponding amine as long as only one equivalent of [I,I-bis(trifluoroacetoxy)iodo]benzene is used.

The acidic nature of the reagent is important; the trifluoroacetic acid liberated in the reaction catalyzes hydrolysis of the intermediate isocyanate, and also ensures that the amine which is formed is protonated and cannot react with the isocyanate to give urea by-products. The reaction can be accelerated by addition of pyridine to an observed pH of about 3.5, and is retarded by added acid or trifluoroacetate ion.^{9b,10} In the present procedure pyridine was not employed, since the reaction in its absence proceeds with a satisfactory rate.

1. Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclobutylamine hydrochloride (8); Cyclobutanamine hydrochloride (9);
(6291-01-6)

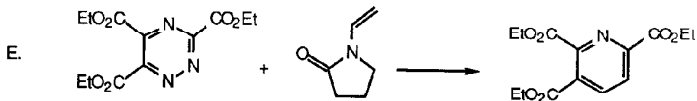
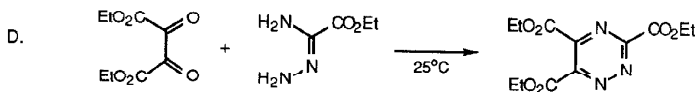
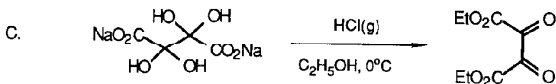
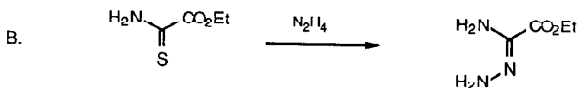
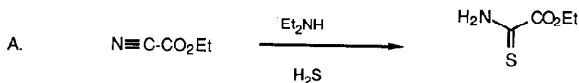
[I,I-Bis(trifluoroacetoxy)iodo]benzene: Iodine,
phenylbis(trifluoroacetato-0-)- (9); (2712-78-9)

Cyclobutanecarboxamide (8,9); (1503-98-6)

Cyclobutanecarboxylic acid (8,9); (3721-95-7)

Ethyl chloroformate: Formic acid, chloro-, ethyl ester (8); Carbonochloridic
acid, ethyl ester (9); (541-41-3)

PREPARATION AND INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF AN
ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: TRIETHYL
1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE
(1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester)



Submitted by Dale L. Boger, James S. Panek, and Masami Yasuda.¹

Checked by Pauline J. Sanfilippo and Andrew S. Kenda.

1. Procedure^{2a}

Caution! Hydrogen sulfide is highly toxic and a stench. Steps A and B must be run in an efficient fume hood.

A. *Ethyl thioamidooxalate*.³ A 100-mL, round-bottomed flask is fitted with a magnetic stirring bar. Ethyl cyanoformate (20 g, 0.20 mol, Note 1) in benzene (25 mL) is added to the reaction vessel and the mixture is cooled to 0°C with an ice bath. Diethylamine (Note 2, 0.4 g, 5.5 mmol, 0.57 mL) is added to the stirring reaction mixture (0°C) and hydrogen sulfide (Note 3) is then bubbled into the reaction for an additional 15-20 min. The reaction mixture is allowed to stir at 25°C (14-16 hr). The crude product is collected by filtration (Note 4) and washed with benzene (2 x 3 mL) to give 20.96 g (78%) of pure ethyl thioamidooxalate. The filtrate is concentrated under reduced pressure and the crude product subjected to chromatography on silica gel (30% ether-hexane eluant) to give an additional 1.57 g of ethyl thioamidooxalate. The total amount of ethyl thioamidooxalate isolated as a bright yellow solid is 22.53 g (84%); mp 63-66°C (Note 5).

B. *Ethyl oxalamidrazonate*. A 1-L, round-bottomed flask is equipped with a magnetic stirring bar and fitted with a 125-mL addition funnel. A solution of anhydrous hydrazine (4.8 g, 0.15 mol) in ethanol (75 mL) is added dropwise (10 min) to a stirred solution of ethyl thioamidooxalate (20.0 g, 0.15 mol) in ethanol (450 mL) at 25°C. The reaction mixture is stirred at 25°C (3.0 hr). The solvent is removed under reduced pressure and the reddish orange solid is triturated with ethanol (350 mL). The ethanolic solution containing the oxalamidrazonate is concentrated under reduced pressure to afford 13.90 g (71%) of ethyl oxalamidrazonate as a yellow solid (Note 6).

C. *Diethyl dioxosuccinate*. A 1-L, round-bottomed flask equipped with a magnetic stirring bar is charged with dihydroxytartaric acid disodium salt hydrate (100 g, 0.44 mol, Note 7) and absolute ethanol (750 mL, Note 8). The suspension is cooled to 0°C with an ice bath and anhydrous hydrogen chloride gas (Note 9) is bubbled into the reaction mixture with stirring (0°C, approximately 30 min). The reaction mixture is stoppered and placed in the refrigerator for 72 hr. The mixture is filtered using a Büchner funnel and the filtrate is concentrated under reduced pressure. The crude diethyl dioxosuccinate is distilled under reduced pressure to afford 39.60 g (44%) of pure diethyl dioxosuccinate (Note 10), bp 109-116°C (6-8 mm); lit.⁴ bp 109-114°C (6 mm).

D. *Triethyl 1,2,4-triazine-3,5,6-tricarboxylate*. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, 500-mL addition funnel and a nitrogen inlet. A solution of ethyl oxalamidrazonate (11.6 g, 88.0 mmol) in absolute ethanol (350 mL) is added dropwise (40-45 min) to a stirring solution of diethyl dioxosuccinate (23.1 g, 114.0 mmol) in absolute ethanol (86 mL) at 25°C under nitrogen. After the addition is complete the reaction mixture is stirred at 25°C (16 hr). A reflux condenser is fitted onto the three-necked, round-bottomed flask and the reaction mixture is warmed at reflux for 2.0 hr. The reaction mixture is cooled and the solvent is removed under reduced pressure. Purification of the product is effected by gravity chromatography (Note 11) on a 5.20 x 40.0-cm column of silica gel (10-40% ether-hexane gradient elution), collecting 100-mL fractions. The fractions are analyzed by thin-layer chromatography on silica gel (40% ether-hexane eluant). The fractions containing product are combined and the solvent is removed under reduced pressure to afford 14.70 g (56%) of pure triethyl 1,2,4-triazine-3,5,6-tricarboxylate as a viscous, yellow oil² (Note 12).

E. *2,3,6-Tricarboethoxypyridine*. A 50-mL, round-bottomed flask is fitted with a magnetic stirring bar and a reflux condenser. Triethyl 1,2,4-triazine-3,5,6-tricarboxylate (1.49 g, 5.0 mmol) and chloroform (22.7 mL, Note 13) are added to the reaction vessel. N-Vinyl-2-pyrrolidone (2.22 g, 20 mmol, 2.3 mL, Note 14) is added to the solution and the reaction mixture is warmed at 60°C under an atmosphere of nitrogen for 26 hr. The solvent is removed under reduced pressure and the crude product subjected to gravity chromatography (Note 11) on a 2.7 x 32-cm column of silica gel (40-50% ether-hexane gradient elution), collecting 50-mL fractions. The fractions are analyzed by thin-layer chromatography on silica gel (50% ether-hexane eluant). The fractions containing product are combined and the solvent is removed under reduced pressure to afford 1.01-1.35 g (68-92%) of 2,3,6-tricarboethoxypyridine as a yellow oil (Note 15).

2. Notes

1. The submitters employed, without purification, ethyl cyanofornate purchased from Aldrich Chemical Company, Inc.
2. The submitters employed, without purification, diethylamine purchased from Aldrich Chemical Company, Inc.
3. Hydrogen sulfide gas was purchased from Burnox, Kansas City, MO. This reaction should be run in a fume hood.
4. In some instances, it is necessary to cool the flask (ice bath) containing the ethyl thioamidooxalate to promote crystallization of the product.

5. The product has the following spectral properties: ^1H NMR (CDCl_3) δ : 1.39 (t, 3 H, $J = 8$, CH_3), 4.33 (q, 2 H, $J = 8$, CH_2), 7.30-8.30 (br s, 2 H, NH_2), mp 63-66°C, lit.² mp 64-65°C.

6. *Caution: This reaction should be carried out in a fume hood. Ethyl oxalamidrazonate cannot be stored in solution for prolonged periods of time.*

7. The submitters employed dihydroxytartaric acid disodium salt hydrate purchased from Aldrich Chemical Company, Inc.

8. Ethanol was dried by distillation from magnesium turnings immediately before use.

9. Anhydrous hydrogen chloride gas purchased from Burnox, Kansas City, MO. was employed.

10. The ^{13}C NMR spectrum of this compound is as follows: ^1H NMR (CDCl_3) δ : 1.36 (t, 3 H, $J = 8$, CH_3), 4.44 (q, 2 H, $J = 8$, CH_2).

11. The checkers used flash chromatography for these steps.

12. The spectral properties of this product (orange oil) are as follows: ^1H NMR (CDCl_3) δ : 1.45 (t, 3 H, $J = 7$, CH_3), 1.48 (t, 3 H, $J = 7$, CH_3), 1.51 (t, 3 H, $J = 7$, CH_3); 4.38-4.68 (3 overlapping q, 6 H, three CH_2); IR (film) ν_{max} cm^{-1} : 2986, 1757, 1738, 1518, 1468, 1408, 1383, 1302, 1217, 1177, 1155, 1099, 1017, 857.

13. The submitters employed chloroform obtained from Fisher Chemical Co.

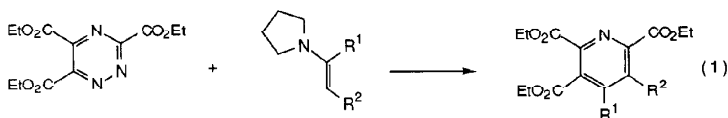
14. The submitters employed, without purification, N-vinyl-2-pyrrolidone obtained from GAF Corporation.

15. The spectral properties of the product are as follows: ^1H NMR (CDCl_3) δ : 1.38 (t, 3 H, $J = 7$, CH_3), 1.41 (t, 3 H, $J = 7$, CH_3), 1.43 (t, 3 H, $J = 7$, CH_3), 4.38 (q, 2 H, $J = 7$, CH_2), 4.44 (q, 2 H, $J = 7$, CH_2), 4.47 (q, 2 H, $J = 7$, CH_2), 8.16 (d, 1 H, $J = 8$, aromatic), 8.30 (d, 1 H, $J = 8$, aromatic); IR (film) ν_{max} cm^{-1} : 2906, 1728, 1506, 1570, 1468, 1455, 1406, 1387, 1370, 1321, 1283, 1239, 1152, 1071, 1021, 853, 762.

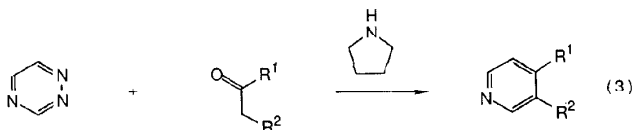
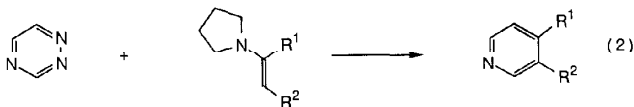
3. Discussion

This procedure describes the preparation of an electron-deficient heterocyclic azadiene suitable for use in inverse electron demand (LUMO_{diene} controlled)⁵ Diels-Alder reactions with electron-rich dienophiles.

Table I^{6,7} details representative examples of the [4 + 2] cycloaddition of triethyl 1,2,4-triazine-3,5,6-tricarboxylate with pyrrolidine enamines and related electron-rich olefins. Cycloaddition occurs across carbon-3 and carbon-6 of the 1,2,4-triazine nucleus, and the nucleophilic carbon of the dienophile attaches to carbon-3 (eq 1). Loss of nitrogen from the initial adduct and aromatization with loss of pyrrolidine affords pyridine products.



Similar reactivity and regioselectivity is observed with the parent system, 1,2,4-triazine (eq 2).^{8a} Reduction of this process to a catalytic Diels-Alder reaction with in situ generation of the pyrrolidine enamine does not alter these observations (eq 3).^{8b}



The number and position of electron-withdrawing substituents on the 1,2,4-triazine nucleus and the reactivity of the electron-rich dienophile determine the mode of cycloaddition (additions across C-5/N-2 as well as C-3/C-6 of the 1,2,4-triazine nucleus have been observed) as well as the regioselectivity.^{8,9} A complete survey of the reported Diels-Alder reactions of 1,2,4-triazines including triethyl 1,2,4-triazine-3,5,6-tricarboxylate has been compiled.¹⁰

1. Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045. Present address: Department of Chemistry, Purdue University, West Lafayette, IN 47907.
2. The procedure described is a modification of a detailed preparation: (a) Ratz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931; (b) For the preparation of 5,6-dimethoxycarbonyl-3-ethoxycarbonyl-1,2,4-triazine, see: Martin, J. C. *J. Org. Chem.* **1982**, *47*, 3761.
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8. (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179; (b) Boger, D. L.; Panek, J. S.; Meter, M. M. *J. Org. Chem.* **1982**, *47*, 895; (c) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782, 5790

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10. Döger, D. L. *Tetrahedron*, **1983**, *39*, 2069.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Triethyl 1,2,4-triazine 3,5,6 tricarboxylate: 1,2,4 Triazine 3,5,6 tricarboxylic acid, triethyl ester (10); (74476-38-3)

Ethyl thioamidooxalate: Oxamic acid, 2-thio-, ethyl ester (8); Acetic acid, aminothioxo, ethyl ester (9); (16982-21-1)

Ethyl cyanoformate: Formic acid, cyano-, ethyl ester (8); Carbonocyanidic acid, ethyl ester (9); (623-49-4)

Ethyl oxalamidrazonate: Acetic acid, hydrazinoimino-, ethyl ester (9); (53085-26-0)

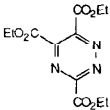
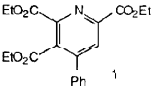
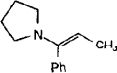
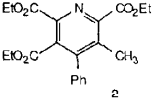
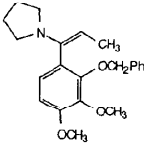
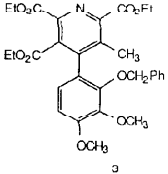
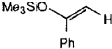
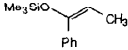
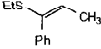

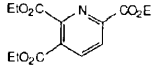
Diethyl dioxosuccinate: Butanedioic acid, dioxo-, diethyl ester (9); (59743-08-7)

Dihydroxytartaric acid, disodium salt hydrate: Butanedioic acid, tetrahydroxy-, disodium salt (9); (866-17-1)

N-Vinyl-2-pyrrolidinone: 2-Pyrrolidinone, 1-vinyl- (8); 2-Pyrrolidinone, 1-ethenyl- (9); (88-12-0)

TABLE I

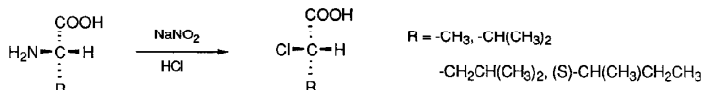
DIELS-ALDER REACTION OF TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE

Dienophile	Conditions: Solv., Temp., Time	Product	% Yield
	CHCl_3 60°C 18 hr	 1	79
	CHCl_3 45°C 8 hr	 2	73
	CHCl_3 45°C 3 hr	 3	59
	CHCl_3 60°C 22 hr	1	84
	CHCl_3 60°C 16 hr	2	0
	CHCl_3 $80-160^\circ\text{C}$ 10-20 hr	3	0
	CHCl_3 60°C 26 hr	 4	92

(S)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY

FROM (S)-2-AMINO ACIDS: (S)-2-CHLOROPROPANOIC ACID

(Propanoic acid, 2-chloro-, (S))



Submitted by Bernhard Koppenhoefer and Volker Schurig.¹

Checked by G. Nagabhushana Reddy and James D. White.

1. Procedure

(S)-2-Chloropropanoic acid. In a 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL dropping funnel and a two-necked adapter fitted with a thermometer and reflux condenser (Note 1), 89.1 g (1 mol) of (S)-alanine (Note 2) is dissolved in 1300 mL of 5 N hydrochloric acid (Note 3). The mixture is cooled to 0°C in an ice/sodium chloride bath (Note 4) and a precooled solution of 110 g (1.6 mol) of sodium nitrite in 400 mL of water is added dropwise at a rate of about 2 mL/min under vigorous stirring and efficient cooling so that the temperature of the reaction mixture is kept below 5°C. After 5 hr, the bath is removed and the reaction is allowed to stand overnight at room temperature (Note 5). The reflux condenser is connected with a water aspirator and the flask is carefully evacuated with stirring for 3 hr to remove nitrogen oxides, whereupon the color changes from yellowish brown to pale yellow. While the mixture is stirred vigorously, 100 g of solid sodium carbonate is added carefully in small portions so as to prevent excessive foaming. The reaction mixture is extracted with four

portions of 400 mL of diethyl ether. The combined ether layers are concentrated to ca. 300 mL using a rotary evaporator at atmospheric pressure. The solution is washed with 50 mL of saturated brine which thereafter is reextracted with three portions of 100 mL of diethyl ether. The combined ethereal solutions are dried for 10 hr over calcium chloride. The ether is distilled off with a rotary evaporator at atmospheric pressure (bath temperature 40 to 50°C). The oily residue is transferred into a distillation flask (rinsing the remainder with small portions of ether) and then fractionally distilled at reduced pressure, the main fraction boiling within a range of 2 to 3°C (i.e., bp 75-77°C at 10 mm) (Note 6) to give 63-71 g (58-65%) of an oil. The colorless oil is sufficiently pure for most purposes (Notes 7 and 8). On prolonged standing in a refrigerator, the oil tends to solidify partially or totally, but the white crystals formed have no sharp melting point. This procedure can be employed for other α -amino acids (see Table and the Discussion).

2. Notes

1. If the procedure is carried out under an atmosphere of nitrogen, oxidation of nitrogen monoxide to nitrogen dioxide is prevented and the reaction mixture remains colorless, but the yield is not improved.

2. The checkers used (S)-alanine of 97% optical purity, purchased from Aldrich Chemical Company, Inc.

The enantiomeric purities of the (S)-amino acids were checked by preparing the corresponding N-trifluoroacetyl amino acid methyl esters, which are resolved into enantiomers by gas liquid chromatography on glass capillary columns coated with the chiral stationary phase 'Chirasil-Val',² (see Table). For this purpose, an aliquot of the aqueous solution, containing about 0.1 to 1 mg of the amino acid, is transferred to a 1-mL vial. Water is removed by a stream of nitrogen and the residue is transformed to the methyl ester hydrochloride (15% hydrochloric acid in methanol, 110°C, 30 min) and finally (after drying in a stream of nitrogen) to the N-trifluoroacetyl derivative (trifluoroacetic anhydride, 110°C, 10 min). This material is dried and dissolved in dichloromethane for GLPC analysis.

The commercially-available (S)-amino acids alanine, valine, leucine and isoleucine usually contained only negligible amounts (a few parts/thousand) of the (R)-antipode, but occasionally up to 2.5% of the (R)-enantiomer has been detected in (S)-alanine and (S)-valine. The (R)-enantiomer is almost completely removed by one recrystallization from water.

3. Concentrated hydrochloric acid is diluted by its own volume with water. Hydrochloric acid (2.4 L, 5 N) is employed for the less soluble (S)-amino acids valine, leucine and isoleucine.

4. A precipitate of the amino acid hydrochloride which formed on cooling is dissolved during the reaction.

5. The less soluble chloroalkanoic acids (R larger than methyl) separate from the solution as an oil.

6. Sometimes a brownish forerun is observed (bp up to 70°C/10 mm for 2-chloropropanoic acid), turning green in a refrigerator and occasionally undergoing vigorous decomposition. It is therefore recommended that distillation be interrupted and the flask containing the forerun removed.

7. If a brownish color or a wide range of the boiling point of the main fraction is observed, redistillation is recommended. Redistillation is necessary for (2S,3S)-2-chloro-3-methylpentanoic acid. Yields are given in Table. Enantiomeric purities (see Table) were determined after conversion to tert-butyl amides (catalyzed by dicyclohexylcarbodiimide, 30 min at 0°C in dichloromethane) by gas liquid chromatography on 'Chirasil-Val'.³ The chiroptical data were determined on double-distilled (S)-2-chloroalkanoic acids. Traces of water (determined by gas liquid chromatography on Porapak using a thermal conductivity detector) cause a significant decrease of the specific rotation.

8. The spectral properties of (S)-2-chloropropanoic acid were as follows: ¹H NMR (CDCl₃) δ: 1.66 (d, 3 H, J = 6.7), 4.40 (q, 1 H, J = 6.7), 12.0 (s, 1 H; this signal may be broadened and shifted upfield due to minimal amounts of water); ¹³C NMR (CDCl₃) δ: 20.9, 52.0, 176.0.

TABLE
(2S)-2-CHLOROALKANOIC ACIDS



Reactant	Substituent R	Yield (%)	bp (°C/mm)	e.e. (%) of Chloro Acid ^a	d_4^{20} (g/cm ⁻³)	$[\alpha]_D^{20}$ (°) ^e
(S)-Alanine	-CH ₃	64 ± 6	75-77/10	95.6 ^b	1.265	-13.98
(S)-Valine	-CH(CH ₃) ₂	62 ± 5	103-105/10	97.7 ^b	1.140	-1.44
(S)-Leucine	-CH ₂ CH(CH ₃) ₂	58 ± 4	113-115/10	95.8 ^c	1.082	-31.73
(2S)-Isoleucine	(3S)-CH(CH ₃)CH ₂ CH ₃	59 ± 6	111-112/10	98.3 ^{c,d}	1.115	-4.78

^aIn each case the starting amino acid was > 99.8% optically pure, as shown by gas chromatography of the trifluoroacetyl methyl esters on Chirasil-Val (Note 2).

^bBy gas chromatography of the tert-butyl amides on Chirasil-Val (Note 7).

^cBy gas chromatography of the tert-butyl amides on (R)-N-lauroyl-1-(1-naphthyl)ethylamine (ref 8).

^dDiastereomeric excess, referring to (2R,3S)-2-chloro-3-methylpentanoic acid. Total composition: 99.0% 2S,3S; 0.8% 2R,3S; 0.2% 2S,3R; approximately 0% 2R,3R. The starting amino acid was contaminated with 0.2% of the 2S,3R.

^eRotations were measured on the neat liquids; specific rotations are given for material of the indicated

3. Discussion

The present procedure is based on the method published by Fu, Birnbaum and Greenstein.⁴ The yields are increased by the very slow addition of an aqueous solution of sodium nitrite to the reaction mixture as well as by a modified work-up procedure, i.e., careful removal of nitrogen oxides and the final decomposition of their adducts with carboxylic acids by buffering with sodium carbonate.

By using high-efficiency capillary gas chromatography with chiral stationary phases (i.e., 'Chirasil-Val'² and (R)-N-lauroyl-1-(1-naphthyl)-ethylamine⁸), it has been possible for the first time to determine the degree of racemization during the substitution reaction which proceeds with overall retention of configuration because of double inversion via an unstable α -lactone.¹⁰ Thus, the maximum degree of inversion amounts to approximately 2.2%, resulting in a 2-chloroalkanoic acid of e.e. 95.6% (see Table) if racemization occurs in the diazotization reaction, and not in the conversion of the free chloroalkanoic acid to the tert-butylamide employed for analysis of the enantiomeric composition.^{3,8} The enantiomeric yields given in the Table represent the *lowest* values found in various experiments. The degree of racemization at carbon atom 2 is strongly affected by the alkyl group R (see Table). Racemization is more pronounced in the case of less hindered primary and secondary carbon atoms adjacent to the stereocenter. It is interesting to note that the degree of racemization observed in the diazotization reaction runs parallel to the degree of racemization observed in aqueous solutions of the amino acids at pH 7.6 at elevated temperature.¹¹

The diazotization in 5 N hydrochloric acid is superior to that in aqua regia⁶ where up to 10% inversion has been observed.¹²

The method described may also be used for the preparation of the corresponding (R)-2-chloroalkanoic acids when starting from unnatural (R)-2-amino acids. For instance, (R)-2-aminodecanoic acid has been obtained in high enantiomeric yield by enzymatic cleavage of the racemic N-chloroacetyl derivative.¹³ For amino acids containing large alkyl side chains diazotization at higher dilution is recommended. For the synthesis of racemic 2-chloroalkanoic acids the diazotization method described here appears more convenient than the direct chlorination of alkanolic acids.¹⁴

2-Chloroalkanoic acids bearing chiral side groups are useful starting materials for the synthesis of chiral alcohols of high enantiomeric purity. Thus, (3S)-3-methylpentanol-1 has been obtained from (2S,3S)-isoleucine via exhaustive lithium aluminum hydride reduction of the chloro acid.¹⁵ Similarly, (3S)-1,3-butanediol has been obtained from (2S,3S)-allothreonine.¹⁶ The time-controlled lithium aluminum hydride reduction of 2-chloroalkanoic acids leads to 2-chloro-1-alkanols (chlorohydrins) which can be cyclized to alkyloxiranes of high enantiomeric purity.¹⁷

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17. Following procedure.

Appendix

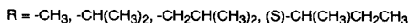
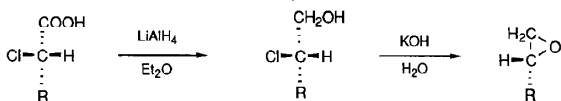
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-2-Chloropropanoic acid: Propionic acid, 2-chloro, (S)- (8);

Propanoic acid, 2-chloro-, (S)- (9); (29617-66-1)

(S)-Alanine: L-Alanine (8,9); (56-41-7)

(R)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY FROM
 (S)-2-CHLOROALKANOIC ACIDS VIA (S)-2-CHLORO-1-ALKANOLS:
 (R)-METHYLOXIRANE
 (Oxirane, methyl- (R)-)



Submitted by Bernhard Koppenhoefer and Volker Schurig.¹

Checked by G. Nagabhushana Reddy and James D. White.

1. Procedure

CAUTION: Methyloxirane is a suspected carcinogen for humans.

(S)-2-Chloropropan-1-ol. Into a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 250 mL dropping funnel, stopper (Note 1) and an efficient reflux condenser fitted with a calcium chloride drying tube, is placed 9.1 g (0.24 mol) of lithium aluminum hydride; 400 mL of dry diethyl ether is added with caution. The slurry is cooled in an ice bath and a solution of 21.7 g (0.20 mol) of (S)-2-chloropropanoic acid (Note 2) in 150 mL of dry diethyl ether is added carefully with vigorous stirring over a 10-min period so that refluxing of the solvent is kept under control. After a total reaction time of 15 min (Note 3), the drying tube is removed and 20 mL of water is added drop by drop (*Caution: vigorous evolution of hydrogen!*) with efficient stirring and cooling (Note 4). The precipitate is dissolved (Note 5) by addition of 0.6 L of 2 N sulfuric acid (Note 6). The layers are

separated, and the aqueous layer is extracted with two 200-mL portions of diethyl ether. The combined ether layers are washed with 50 mL of water, 50 mL of sodium carbonate solution (Note 4) and 50 mL of sodium bicarbonate solution, each aqueous layer being reextracted with two 50-mL portions of diethyl ether (Note 7). The combined ethereal layers are concentrated with a rotary evaporator at atmospheric pressure (bath temperature 40 to 50°C) to approximately 300 mL, dried over sodium sulfate, and concentrated to give an oily residue. Fractional distillation at reduced pressure (Note 8) affords 10.6–11.0 g (56–58%) of a colorless oil. This procedure can be applied to chlorohydrins with other alkyl residues (see Notes 3 and 8, Table I).

(R)-Methyloxirane (Note 9). The reaction is conveniently carried out in a special apparatus (see Figure 1) in order to prevent loss of the volatile oxirane. A 50-mL, narrow-necked vessel (A) is equipped with a magnetic stirrer and a small Claisen stillhead (B), fitted with a thermometer and connected to a small receiver adapter with vacuum connection (C). A 25-mL or 50-mL flask (D) serves as a trap for the oxirane. To prevent clogging of the inlet pipe (E) by solidified reaction product, an appropriate flask (D) is chosen so that the distance between the inlet pipe (E) and the flask (D) is approximately 5 to 10 mm. The vacuum end of the adapter (C) is connected via a stopcock (F), a T-piece carrying a needle valve (G), and a manometer (H) to a water aspirator (I). The reaction vessel (A) is equipped with an ice bath, thermometer and a combined heater and magnetic stirrer which is placed on a jack. After the entire apparatus is connected (F closed), trap (D) is air-cooled in a Dewar (K) which is partially filled with liquid nitrogen, and heat-insulated at the top with cotton. A low-temperature thermometer (L) is placed at the same height near trap (D). The temperature of trap (D) is controlled, by moving the jack to the appropriate height to approximately

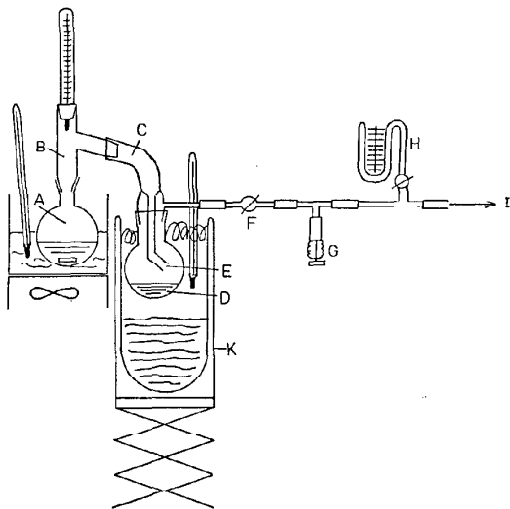


Figure 1. Apparatus for the Preparation of (R)-Methyloxirane.

-80°C. The pressure is adjusted by a needle valve (G) to 100 mm (F remains closed). A solution of 12.3 g (0.22 mol) of potassium hydroxide pellets in 12 mL of water is placed in vessel (A) and cooled to 0°C. Neat (S)-2-chloropropan-1-ol, 11.8 g (0.125 mol), is poured at once into the alkaline solution (Note 10), and the reaction vessel is immediately fitted with still-head (B) and stirred vigorously with efficient cooling. Stopcock (F) is opened occasionally for a short period until the pressure in the closed system is reduced to 100 mm (Note 11). The ice bath is replaced by a water bath at 20°C. As the cyclization reaction proceeds a white precipitate of potassium

chloride is formed. After 10 min, the temperature of the bath is raised slowly to 30°C. Gentle boiling of the oxirane is maintained by cautiously opening stopcock (F) from time to time, attention being paid to the reaction vessel. After a total reaction time of 40 min (Note 12), air is allowed to enter the closed system at the top of the stillhead, and trap (D) is allowed to warm (Note 13) until two liquid phases are formed. The lower phase containing water is transferred via a Pasteur pipette into a small flask (Note 14). Flask (D) containing 5.9 g (81%) of crude (R)-methyloxirane is used in position (A) of the clean, dry apparatus (see Figure 1) for redistillation of the oxirane from calcium hydride. At atmospheric pressure (stopcock F open), flask (A) is cooled to 0°C, whereas trap (D) is kept at room temperature. Calcium hydride is added in small portions over a period of 1 to 2 hr until evolution of hydrogen ceases. Stopcock (F) is closed, trap (D) is cooled and the oxirane is distilled as described. Reduced pressure is applied with great care to avoid too vigorous boiling; 4.7-5.0 g (65-70%) of anhydrous oxirane is obtained as a clear liquid. This procedure can be employed for other oxiranes with slight modifications (see Notes 12 and 14, and Table II).

2. Notes

1. As a safeguard it is recommended that the reaction be performed under nitrogen, using a gas inlet instead of the stopper. The flask should be dry and free of faults.

2. (S)-2-Chloroalkanoic acids are prepared according to the procedure given previously.²

3. A total reaction time of 30 min is needed for more sterically hindered (S)-2-chloroalkanoic acids. Prolonged reaction time should be avoided to prevent hydrogenolysis of the chlorine-carbon bond.

4. Prolonged exposure to alkaline conditions should be avoided to prevent oxirane formation at this step.

5. The aqueous phase is allowed to remain opalescent, to avoid unnecessarily low pH-values.

6. Concentrated sulfuric acid, 60 g, is added to a beaker charged with 540 g of crushed ice. Precooled 2 N sulfuric acid is added to the reaction mixture.

7. Less than 5% of the chloroalkanoic acid is reisolated after acidification of the sodium carbonate phase and extraction with diethyl ether.

8. (S)-2-Chloropropan-1-ol is carefully distilled at atmospheric pressure using a 20-cm Vigreux column. (S)-2-Chloro-3-methylbutan-1-ol, (S)-2-chloro-4-methylpentan-1-ol and (2S,3S)-2-chloro-3-methylpentan-1-ol are distilled under reduced pressure with a spinning-band column or a 'Spaltrohr-column' (approximately 50 theoretical plates, supplier: W. G. Fischer, D-5309 Meckenheim, FRG), see Table I. The main fractions are > 99% pure by GLC (OV 17 on Chromosorb P AW-DMCS). Because of the low boiling points of the oxiranes, diethyl ether should be completely removed from the chlorohydrins.

9. The synthesis should be carried out in a well-ventilated hood.
CAUTION: Methyloxirane is a suspected carcinogen for humans.

10. The amount of chlorohydrin used is determined from the weight remaining in the original flask (approximately 1 g).

11. During the course of the reaction, stopcock (F) should remain closed except for short periods in order to avoid loss of the volatile oxirane. There is no danger of excess pressure in the closed system as long as trap (D) is cooled efficiently.

12. The chlorohydrins show different rates of cyclization, reflecting the steric hindrance of residue R. The most vigorous reaction is observed in the case of (S)-2-chloropropan-1-ol ($R = CH_3$); only 30°C at 100 mm is required. For (R)-isopropyloxirane, the temperature of the bath is raised slowly to 50°C, and after 40 min to 60°C, while the pressure is reduced to 50 mm for an additional 5 min. For the higher boiling oxiranes, e.g., (R)-isobutyloxirane and (S)-sec-butyl-(R)-oxirane [(2R,3S)-3-methyl-1,2-epoxybutane], the temperature is raised slowly to 60°C within 1 hr, while the pressure is reduced carefully to 30 mm.

13. Build-up of pressure of methyloxirane is prevented by briefly opening the apparatus from time to time.

14. For methyloxirane, the binary system with water has been studied in detail.³ By careful operation during the distillation, water is largely retained in the original flask (A). The racemate melts at -112°C, but the hydrate $C_3H_6O(H_2O)_{16}$ (mp -3°C) may solidify in the inlet tube (E). In the case of higher boiling oxiranes, substantial amounts of water are co-distilled. After removal from flask (D), the aqueous phase may be saturated with sodium chloride. Thereby a second portion of the oxirane (approximately 0.2 g) is separated and combined with the main portion in flask D.

3. Discussion

The method described here illustrates the transformation of optically active 2-chlorocarboxylic acids, which are readily available from 2-amino acids,² via 2-chloroalkan-1-ols to alkyloxiranes with inversion of configuration at the stereocenter. Thus (R)-methyloxirane is prepared from (S)-alanine, (R)-isopropyloxirane from (S)-valine, (R)-isobutyloxirane from

(S)-leucine, and (S)-sec-butyl-(R)-oxirane from (2S,3S)-isoleucine, respectively. This useful three-step route complements the synthesis of (S)-alkyloxiranes from (S)-2-amino acids via (S)-2-hydroxy acids,^{4,5} with retention of configuration at the stereocenter.

The stereoselective conversion of chlorohydrins into diols via oxiranes as intermediates in aqueous potassium hydroxide solution was originally described by Fickett, Garner, and Lucas.⁶ In the present procedure, the oxiranes are distilled off as they are formed to prevent subsequent ring-opening. Among different reaction conditions investigated,⁷ the procedure given here appears to be most convenient, and is accompanied by almost no racemization (Table II). The enantiomeric purities of the oxiranes are determined directly with high precision by complexation gas chromatography on optically active metal chelates (e.g., Ni(II) bis(2-heptafluorobutyryl)-(S)-4-methylthujan-3-onate⁸ or Mn(II) bis(3-heptafluorobutyryl)-(R)-camphorate,⁷ respectively). Depending on the chemical structure of the chloro acids used,² the degree of inversion of configuration is less than 0.5% for R = methyl, isopropyl and (S)-sec-butyl, and approximately 1.5% for R = isobutyl. In the latter case, prolonged exposure of the oxirane to the reaction mixture leads to increased racemization. (R)- and (S)-Methyloxirane have been synthesized with retention of configuration from (R)- and (S)-propane-1,2-diol, respectively, by cyclization of the bromoacetates,⁹⁻¹¹ which seems to be superior to the route via bromohydrins.¹² Starting from commercially available (S)-ethyl lactate,⁹ other groups have employed different routes to (S)-methyloxirane^{13,14} ($[\alpha]_D^{25}$ -12.5° (neat)¹³ and to (R)-methyloxirane^{15,16} ($[\alpha]_D^{24}$ +13.9° (neat),¹⁵ $[\alpha]_D^{20}$ +13.4° (neat),¹⁷ $[\alpha]_D^{22}$ +13.0° (neat),¹⁶ $[\alpha]_D^{25}$ +11.97° (neat)¹⁸). The apparent deviations of these specific rotations from the maximum optical rotation extrapolated for the pure enantiomer may be ascribed

to lack of enantiomeric purity of the substances described, and to inappropriate optical rotation measurements (error in the density, chemical impurities). Enantiomeric impurities in the oxirane can also originate from the starting material since variable fractions of (R)-ethyl lactate (up to 5%) have been detected in commercial (S)-ethyl lactate by gas chromatography on D-Chirasil-Val.¹⁹ The enantiomeric purity of the chiral starting material must be established with certainty in any "chiral pool" transformation.

The "chiral pool" approach appears at present to be superior to other methods of access to optically active alkyl-substituted oxiranes, e.g., enzymatic²⁰⁻²² and nonenzymatic²³ epoxidation of prochiral olefins, chromatographic resolution experiments^{11,24} and kinetic resolution methods.^{8,25,26a} Halohydrins and oxiranes of high enantiomeric purity have recently been obtained by diastereoselective synthesis.^{26b} As reviewed previously,¹⁰ a variety of optically active compounds have been synthesized from (R)- and (S)-methyloxirane. Additional examples are macrolides,²⁷⁻²⁹ alcohols,³⁰⁻³² amino alcohols,^{20,33} 1-chloro-2-alkanols³⁴ and thiiranes.^{17,35} The potential of higher, alkyl-substituted oxiranes as building blocks in chiral synthesis awaits its full exploitation. (S)-Ipsenol has been synthesized from (S)-isobutyloxirane,^{36,37} which is also available from D-mannitol.^{37,38} By stereoselective ring-opening reactions, optically active oligomers (crown ethers)³⁹ and polymers are conveniently prepared.

TABLE I
(2S)-2-CHLOROALKAN-1-OLS (CHLOROHYDRINS)



Substituent R	Yield (%)	bp ($^{\circ}\text{C}/\text{mm}$)	n_D^{20} (g/cm^3)	$[\alpha]_D^{20}$ ($^{\circ}$) ^a
-CH ₃	56	131/725	1.110 ₁	+17.8
-CH(CH ₃) ₂	70	91/50	1.044 ₂	+ 3.6
-CH ₂ CH(CH ₃) ₂	64	92/30	1.005 ₃	-48.8
(S)-CH(CH ₃)CH ₂ CH ₃	56	75/10	1.028 ₆	- 7.6

^aRotations were measured on the neat liquids.

TABLE II
(2R)-ALKYLOXIRANES (1,2-EPOXYALKANES)



Substituent R	Yield(%) ^a	bp(°C/mm) ^b	e.e.(%)	d_4^{20} (g/cm ³)	$[\alpha]_D^{20}$ (°) ^c
-CH ₃	81/67	34/728	94.6±0.4 ^d	0.8309	+13.12
-CH(CH ₃) ₂	93/87	82/730	97.4±0.2 ^e	0.8201	- 4.46
-CH ₂ CH(CH ₃) ₂	84/78	108/730	93.0±0.4 ^e	0.8241	+20.47
(S)-CH(CH ₃)CH ₂ CH ₃	79/73	109/726	97.4±0.2 ^{d,f}	0.7598	+14.4

^aFirst number: crude reaction product (organic layer); second number: final yield after redistillation.

^bDetermined in a separate experiment.

^cRotations were determined on neat samples; specific rotations are for material of the indicated e.e.

^dDetermined by complexation gas chromatography on Ni(II) bis(2-heptafluorobutyryl-(S)-4-methylthujan-3-onate) (ref 8).

^eDetermined as Mn(II) bis(3-heptafluorobutyryl-(R)-camphorate) (ref 7).

^fDiastereomeric excess, referring to (2S,3S)-1,2-epoxy-3-methylpentane, (S)-sec-butyl-(R)-oxirane as impurity. Composition: 98.5 ± 0.1% 2R,3S; 1.3 ± 0.1% 2S,3S; 0.2 ± 0.1% 2R,3R. approximately 0% 2S,3R.

1. Institut für Organische Chemie der Universität, Auf der Morgenstelle 18, D-7400 Tübingen, FRG. We thank Mrs. D. Wistuba, University of Tübingen, for determination of the enantiomeric purity of the oxiranes, and Deutsche Forschungsgemeinschaft and Fonds der chemischen Industrie for financial support.
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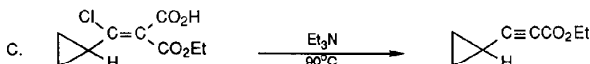
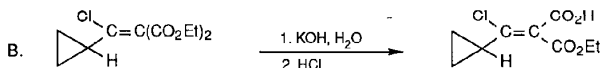
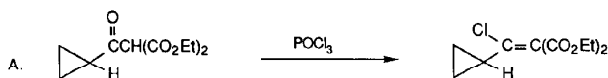
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

- (R)-Methyloxirane: Propylene oxide, (R)-(+)-(8); Oxirane, methyl-, (R)-(9); (15448-47-2)
- (S)-2-Chloropropanoic acid: Propionic acid, 2-chloro-, (S)- (8); Propanoic acid, 2-chloro-, (S)- (9); (29617-66-1)
- (S)-2-Chloropropan-1-ol: 1-Propanol, 2-chloro-, (S)-(+)- (8); 1-Propanol, 2-chloro-, (S)- (9); (19210-21-0)

UTILIZATION OF β -CHLORO ALKYLIDENE/ARYLIDENE MALONATES IN
ORGANIC SYNTHESIS: SYNTHESIS OF ETHYL CYCLOPROPYLPROPIOLATE



Submitted by Osmo Hormi.¹

Checked by David Gare and Clayton Heathcock.

1. Procedure

A. *Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate*. A 1-L, two-necked flask, equipped with magnetic stirrer, reflux condenser and a dropping funnel is charged with 166 g (0.73 mol) of diethyl cyclopropylcarboxymalonate (Note 1) and 0.5 kg of phosphorus oxychloride (Note 2). The flask is cooled with a water bath, stirring is started and 135 g (0.73 mol) of tributylamine (Note 3) is added from the dropping funnel. The reaction is exothermic. When the addition is complete, the dropping funnel is replaced by a glass stopper and the water bath is replaced by an oil bath. The mixture is heated at 110°C with stirring for 5-6 hr.

Excess phosphorus oxychloride is removed as well as possible with a rotary evaporator under reduced pressure. The residue is cooled to room temperature and 300 mL of diethyl ether is added. The mixture is poured into a separatory funnel. Hexane is added until the two phases separate cleanly and the funnel is shaken vigorously. The phases are separated and the lower layer is extracted with three 250-mL portions of ether (Note 4). The combined organic layers are washed with 300 mL of cold aqueous 10% hydrochloric acid and 200 mL of aqueous 5% sodium hydroxide (Note 5) and then concentrated carefully with a rotary evaporator to give 136-156 g (70-87%) of crude diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate.²

B. The crude chloromalonate is dissolved in 100 mL of 95% ethanol and transferred to a 1-L, round-bottomed flask equipped with a magnetic stirring bar. Stirring is begun and a solution of potassium hydroxide in 350 mL of 95% ethanol (0.0035 mol of potassium hydroxide per gram of chloromalonate) (Note 6) is added dropwise from an addition funnel. A slightly exothermic reaction is noted. After the addition is complete, the mixture is stirred for 3 hr (or until the mixture is neutral to litmus, Note 7). Excess ethanol is removed with a rotary evaporator under reduced pressure and the residue is dissolved in 300 mL of water and extracted with 350 mL of ether (Note 8). The phases are separated and some ice is added to the aqueous phase. The cooled, aqueous phase is acidified with concentrated hydrochloric acid and extracted with three 300-mL portions of ether. The ether phase is dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator to give 72-94 g (70-80%) of crude monoester.

C. *Ethyl cyclopropylpropiolate*. The crude product is transferred to a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. A solution of 0.70 mL of triethylamine (Note 9) per gram of

crude monoester from part B in about 200 mL of toluene is added. The mixture is heated using an oil bath at 90°C with stirring until the evolution of carbon dioxide has subsided, and is then heated for another hour (Note 10). The mixture is cooled to room temperature, washed with 300 mL of aqueous 10% hydrochloric acid (Note 11) and finally with 300 mL of aqueous 5% sodium carbonate. The organic layer is dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator. Fractional distillation of the residue gives the product, 87-95°C at 10 mm. The yield of the final step is 30-46 g (66-78%); the overall yield is 33-54% (Note 12).

2. Notes

1. Diethyl cyclopropylcarbonylmalonate is prepared by the procedure of Price and Tarbell^{3a} or Reynolds and Hauser.^{3b} On scale-up the checkers found that a slight modification is necessary: The procedure of Price and Tarbell was used:^{3a} 45 g (1.9 mol) of magnesium turnings, 1 mL of carbon tetrachloride, and approximately 20 mL of a solution of 281 mL (269 g, 1.9 mol) of diethyl malonate in 148 mL of absolute ethanol were combined. After the reaction begins, the addition of diethyl malonate solution is completed so that the reaction is maintained at a fairly vigorous rate. If the reaction subsides prior to the completion of the addition of the diethyl malonate solution, the addition is interrupted and a portion (300 to 400 mL) of the specified 550 mL of dry ether is added cautiously until the reaction resumes, whereupon the addition of the diethyl malonate solution is resumed. After the remainder of the diethyl malonate solution has been added and the reaction mixture cooled, the remaining dry ether is added cautiously and the mixture is worked-up as described^{3a} using 350 mL of dry benzene. The residue is

dissolved in 550 mL of dry ether and treated as described by Reynolds and Hauser^{3b} with 168 mL (194 g, 1.9 mol) of cyclopropanecarboxylic acid chloride in 230 mL of dry ether. After the addition is completed, an additional 40 mL of dry ether is added and the mixture is cooled and worked up as described^{3b} using 2L of aqueous 25% sulfuric acid, 800 mL of ether, 600 mL of saturated aqueous sodium bicarbonate, 200 mL of water, and 100 mL of brine. The crude product is distilled (85-95°C; 0.05 mm) and 362 g (1.6 mol, 86%) of a clear liquid is obtained. ¹H NMR δ : 1.01 (m, 2 H), 1.20 (m, 2 H), 1.31 (t, 6 H, J = 7.1), 2.12 (tt, 1 H, J = 4.5, 7.8), 4.28 (q, 4 H, J = 7.1), 4.58 (s, 1 H).

2. Commercial phosphorus oxychloride was used without purification.

3. Commercial tributylamine was used without purification.

4. Extraction with a mixture of ether and hexane is repeated until ether and the lower layer readily separate.

5. Tributylamine is liberated from the lower layer by addition of sodium hydroxide.

6. Commercial potassium hydroxide (min 85.5% of potassium hydroxide) was used. The yield is based on potassium hydroxide.

7. Dilution of 1 mL of the mixture in 5 mL of water gave pH 7-8.

8. The ether phase is dried with anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to give 32-46 g of recovered starting material.

9. Commercial triethylamine was used without purification.

10. The checkers found that this process requires approximately 24 hr.

11. Triethylamine is liberated from the water phase by addition of sodium hydroxide.

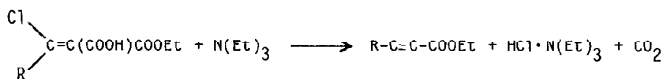
12. Cyclopropylpropionic acid ethyl ester has the following spectra: ^1H NMR (CCl_4) δ : 0.84 and 0.93 (4 H, ring CH_2), 1.25 (t, 3 H, CH_3 ester), the ring-CH is hidden under the ester CH_3 -triplet, 4.05 (q, 2 H, CH_2 ester); IR (CCl_4) cm^{-1} : 2220 ($\text{C}\equiv\text{C}$), m, 1710 ($\text{C}=\text{O}$), s, 1255 ($\text{C}-\text{O}-\text{C}$), s, 1030-1040 two bands (cyclopropyl), m, and 860-880 two bands (cyclopropyl), w; MS: M (calculated for $\text{C}_8\text{H}_{10}\text{O}_2$) 130.060, M^+ is not readily detected, 94 (20%), 93 (100%), 66 (65%), 65 (53%), 63 (10%), 53 (15%), 40 (10%).

3. Discussion

Substituted cyclopropyl rings conjugated with a triple bond system have recently received attention as C_5 building blocks.⁴ The procedure described here is a modification of the decarboxylation-elimination reaction for the preparation of α,β acetylenic acids from enol sulfonates of acyl malonates.^{5,6,7} Addition of aqueous alkali to the enol sulfonate of diethyl cyclopropylcarbonylmalonate gives cyclopropylpropionic acid, but the yield is low.

The major advantages of this procedure over the enol sulfonate procedure lie in the availability of diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate from the corresponding acylmalonate and phosphorus oxychloride, and the fast, homogeneous, decarboxylative elimination reaction of the triethylamine salt of the half-ester in dry organic solvents. The conditions described here, with slight modifications (overnight treatment), have been used for a variety of β -chloro alkylidene/arylidene malonates as shown in Table I.

TABLE I

 α,β -ACETYLENIC ESTERS FROM β -CHLORO ALKYLIDENE MALONATES

R	Yield
Phenyl	80%
2-Thienyl	90%
p-NO ₂ -C ₆ H ₄	70%
Isopropyl	67%
tert-Butyl	70%

Sometimes the acetylenic ester rearranges to the corresponding allenic ester. For example, when the triethylamine salt of 3-chloro-2-ethoxycarbonyl-4-phenyl-2-hexenoic acid is refluxed in toluene, the allenic ester and acetylenic ester are obtained in a ratio of 3:7 (total yield 70%). There are alternative routes to cyclopropylpropionic acids and esters, such as adding butyllithium to corresponding acetylenes and treating the product with carbon dioxide or methyl chloroformate.⁴

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

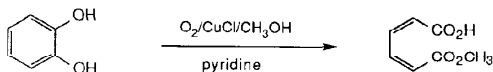
Diethyl cyclopropylcarbonylmalonate: Malonic acid, (cyclopropylcarbonyl)-, diethyl ester (8); Propanedioic acid, (cyclopropylcarbonyl)-, diethyl ester (9): (7394-16-3)

Diethyl malonate: Malonic acid, diethyl ester (8); Propanedioic acid, diethyl ester (9): (105-53-3)

OXIDATIVE CLEAVAGE OF AN AROMATIC RING: *cis,cis*-MONOMETHYL

MUCONATE FROM 1,2-DIHYDROXYBENZENE

(2,4-Hexadienedioic acid, monomethyl ester. (Z,Z)-)



Submitted by Donald Bankston.¹

Checked by Won Hun Ham and Leo A. Paquette.

1. Procedure

A. *cis,cis*-Monomethyl muconate. A 1000-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer and an addition funnel (Note 1, Figure 1). The flask is charged with 400 mL of pyridine, 5 mL (0.12 mol) of methanol, and 9.9 g (0.10 mol) of cuprous chloride under an atmosphere of nitrogen (Note 2). The resultant yellow solution is stirred vigorously at room temperature until the cuprous chloride dissolves (Note 3). The nitrogen is removed and oxygen is bubbled into the flask below the surface of the liquid for approximately 30 min (Note 4). A solution, composed of 1000 mL of pyridine, 5.5 g (0.05 mol) of 1,2-dihydroxybenzene (catechol), and 5 mL (0.12 mol) of methanol, is degassed and slowly added to the flask over a 2-hr period with efficient stirring (Note 5). The reaction mixture is stirred for an additional 30 min before the pyridine is removed at reduced pressure. The dark green residue is dissolved in 300 mL of ethyl ether (Note 6) and

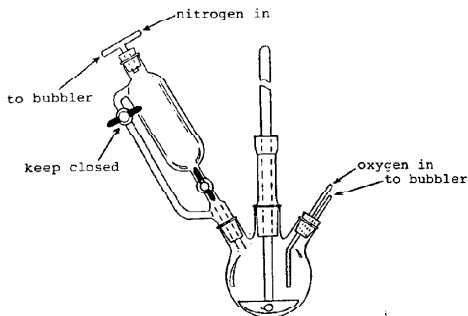
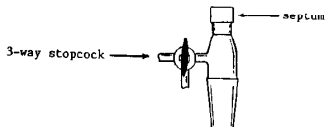


Figure 1

300 mL of 6 N hydrochloric acid; this solution is stirred for 10 min, filtered over Celite, and the organic layer is isolated. The ether is removed at reduced pressure and the resultant brown residue is boiled sequentially with six 50-mL portions of hexane (Note 7). The hot liquid is carefully decanted, leaving behind most of the dark residue. The yellow to colorless solid is crystallized from hot hexane (or methanol) to yield 5.6-6.2 g (71-80%) of colorless needles, mp 80-81°C (Note 8).

2. Notes

1. The checkers employed an alternate device of the following type and



introduced the methanolic catechol solution subsequently via syringe.

2. Pyridine (Mallinckrodt Inc., reagent grade) was distilled over potassium hydroxide, bp 114-116°C. Cuprous chloride was prepared fresh,² washed with anhydrous methanol (distilled from magnesium metal), and dried under reduced pressure. Methanol (Fisher Scientific Company, purified grade) was dried over molecular sieves. The concentration of the methanol should be within the range of 3-8 mol/mol of catechol^{3,4} and anhydrous conditions are necessary.⁴

3. Dissolution requires 1.5-2 hr. If the solution is not properly degassed, it will turn green prematurely. The green color indicates that oxygen absorption by the cuprous chloride-pyridine complex has occurred, but it also means that any undissolved cuprous chloride has been oxidized. Therefore, nitrogen should be bubbled into the flask at a brisk rate and stirring should not commence until addition of the cuprous chloride is complete.

4. As oxygen is introduced into the flask the solution becomes dark green and slightly viscous.

5. Catechol was purchased from Fisher Scientific Company (resublimed). The addition funnel should be charged with a nitrogen atmosphere throughout addition to obviate oxidation of the catechol.

6. Ethyl ether was purchased from Mallinckrodt Inc. (analytical grade); methylene chloride may be substituted, but the monomethyl ester is more soluble in ether. At least two other extractions will be necessary to optimize the yield when methylene chloride is used.

7. Hexane was purchased from Fisher Scientific Company (technical grade).

8. The spectral properties are as follows: ¹H NMR (300 MHz, CCl₄) δ: 3.74 (s, 3 H); 5.88-6.09 (m, 2 H); 7.75-8.26 (m, 2 H); 11.29 (s, 1 H).

3. Discussion

Phenol also undergoes oxidative cleavage in the presence of $O_2/CuCl/pyridine$ and methanol to give cis,cis-monomethyl muconate, but the yield is not high.^{4,5} It has also been observed that catechol, under anaerobic conditions, reacts with cupric methoxy chloride in pyridine containing water and methanol to give cis,cis-monomethyl muconate in high yield.⁶ Catechol and phenol may also be converted to cis,cis-muconic acid by a metal-catalyzed peracetic acid oxidation;⁷ subsequently, treatment with diazomethane gives the monomethyl or dimethyl ester.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

cis,cis-Monomethyl muconate: 2,4-Hexadienedioic acid, monomethyl ester,
(Z,Z)- (9); (61186-96-7)

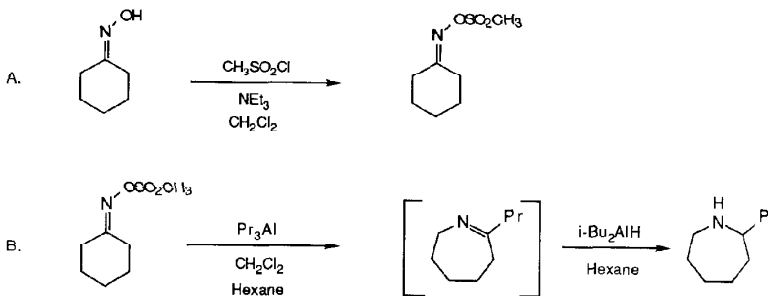
1,2-Dihydroxybenzene: Pyrocatechol (8); 1,2-Benzenediol (9); (120-80-9)
Methanol (8,9); (67-56-1)

Cuprous chloride: Copper chloride (8); Copper chloride (CuCl) (9);
(7758-89-6)

PREPARATION OF 2-PROPYL-1-AZACYCLOHEPTANE

FROM CYCLOHEXANONE OXIME

(1H-Azepine, hexahydro-2-propyl-, (\pm))



Submitted by Keiji Maruoka, Shuichi Nakai, and Hisashi Yamamoto.¹

Checked by Jeffrey Doney and Clayton H. Heathcock.

1. Procedure

Caution! Part B of this procedure should be carried out in a well-ventilated hood to prevent exposure to methanethiol, a side-product.

A. *Cyclohexanone oxime methanesulfonate.* A dry, 1-L, two-necked, round-bottomed flask is equipped with a gas inlet, rubber septum, and magnetic stirring bar. The flask is charged with 17.0 g (0.15 mol) of cyclohexanone oxime (Note 1) and flushed with argon, after which 300 mL of dichloromethane followed by 25 mL (0.18 mol) of triethylamine (Note 2) are injected through the septum into the flask. The solution is stirred and cooled to a temperature of -15 to -20°C in a dry ice-carbon tetrachloride bath, while 12.8 mL

(0.165 mol) of methanesulfonyl chloride is added over a 20-min period (Notes 3 and 4). The resulting mixture is stirred at this temperature for 15 min, and poured into 300 mL of ice-water in a 1-L separatory funnel with the aid of three 30-mL portions of dichloromethane to rinse the flask. The lower organic layer is separated, and the aqueous layer is extracted with a 50-mL portion of dichloromethane. The combined extracts are washed successively with 250 mL of cold aqueous 10% hydrochloric acid, 250 mL of saturated sodium bicarbonate, 250 mL of brine, dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator at room temperature to give 27.2-28.8 g of crude solid cyclohexanone oxime methanesulfonate (Note 5). This material is used in part B without purification (Note 6).

B. 2-Propyl-1-azacycloheptane. A dry, 2-L, three-necked, round-bottomed flask is equipped with a variable speed mechanical stirrer, 300-mL pressure-equalizing dropping funnel bearing a gas inlet at its top, and a rubber septum. The apparatus is flushed with argon, after which 243 mL of hexane (Note 7) and 57 mL (0.3 mol) of tripropylaluminum (Note 8) are injected through the septum into the flask. The solution is stirred and cooled to a temperature of -73 to -78°C in a dry ice-methanol bath. The crude cyclohexanone oxime methanesulfonate prepared in Part A is dissolved in 100 mL of dichloromethane, transferred to the dropping funnel, and added to a 1 M solution of tripropylaluminum in hexane over a 30-min period (Note 9). The mixture is allowed to warm to 0°C , stirred for 1 hr, and 225 mL (0.225 mol) of a 1 M solution of diisobutylaluminum hydride in hexane (Note 10) is added at 0°C and the mixture is further stirred at 0°C for 1 hr (Note 11). After addition of 100 mL of dichloromethane and 88.2 g (2.1 mol) of sodium fluoride, 28.4 mL (1.58 mol) of water is injected dropwise at 0°C (Note 12). Vigorous stirring of the resulting suspension is continued for 30 min at room

temperature, and the contents of the flask are filtered with five 30-mL portions of dichloromethane (Note 13). The combined filtrates are evaporated under reduced pressure with a rotary evaporator. Distillation of the residual liquid under reduced pressure affords 11.3-12.2 g (53-58%) of 2-propyl-1-azacycloheptane as a colorless liquid, bp 79-81°C (18 mm) (Notes 14 and 15).

2. Notes

1. Reagent-grade cyclohexanone oxime, purchased from Wako Pure Chemical Industries, Ltd. (Japan), was used as received. The checkers used material obtained from the Aldrich Chemical Company, Inc. A suitable material may be prepared according to the procedures in *Organic Syntheses*.²

2. Both reagent-grade dichloromethane and triethylamine were dried and stored over Linde type 4 Å molecular sieves.

3. The solution turns to a white suspension after half of the methanesulfonyl chloride is added; methanesulfonyl chloride, available from Tokyo Kasei Kogyo Company, Ltd. (Japan), was used without any purification.

4. The checkers found that an addition time of 40 min is required to maintain the temperature of the reaction mixture below -15°C.

5. If a crude oil was obtained at this stage, it can be solidified by cooling.

6. The reaction in Part A proceeds in almost quantitative yield.³ Accordingly the crude cyclohexanone oxime methanesulfonate can be used without any purification. Prolonged standing at room temperature may cause serious decomposition. The crude material may be stored in a freezer, or as a dichloromethane solution in a refrigerator, and can be recrystallized from ether-hexane to give the white solid (mp 43-45°C).⁴

7. Reagent-grade hexane was dried and stored over sodium.

8. Neat tripropylaluminum of 96% purity was supplied in a metal cylinder from Toyo Stauffer Chemical Company, Ltd. (Japan). This reagent is contaminated by 1.2% of triethylaluminum, 2.2% of triisobutylaluminum, and other compounds. Neat tripropylaluminum is also available from Aldrich Chemical Company, Inc. Since neat tripropylaluminum is pyrophoric and reacts violently with oxygen and water, the syringe should be washed with hexane immediately after addition.

9. The checkers found that an addition time of 60 min is required to maintain the temperature of the reaction mixture below -73°C .

10. Diisobutylaluminum hydride in hexane was available from Aldrich Chemical Company, Inc. and Kanto Chemical Company, Inc. (Japan).

11. Methanethiol is generated as a side-product by the reduction of the methanesulfonate with diisobutylaluminum hydride.

12. To avoid excessive foaming at the beginning of the hydrolysis water should be added carefully by syringe. The rate of addition may be increased once the initially vigorous foaming subsides.

13. The sodium fluoride-water work-up offers an excellent method for large-scale preparations, and is generally applicable for product isolation in the reaction of organoaluminum compounds.⁵

14. The elemental analysis and the spectral properties of the product are as follows: Anal. Calcd for $\text{C}_9\text{H}_{19}\text{N}$: C, 76.61; H, 13.47; N, 9.92. Found: C, 76.75; H, 13.74; N, 9.51; IR (liquid film) cm^{-1} : 3320, 2860-2970, 1460, 1165; ^1H NMR (CDCl_3) δ : 0.87-0.94 (3 H, m, CH_3), 1.23-1.82 (13 H, m), 2.54-2.73 (2 H, m, CH_2N), 2.96-3.03 (1 H, m, CHN). A boiling point of $193\text{--}194^{\circ}\text{C}$ at 750 mm has been reported for 2-propyl-1-azacycloheptane.⁶

15. Gas chromatographic analysis using a 25-m PEG-HT capillary column at 80°C indicated a purity of 97% (retention time: 8.1 min) based on tripropylaluminum of 96% purity (Note 8). The unrearranged product, cyclohexylpropylamine (retention time: 6.9 min), was less than 1%.

3. Discussion

This procedure illustrates a new, general method for the one-nitrogen ring expansion of cyclic ketoximes leading to α -alkylated, cyclic, secondary amines.^{4,7} The key step in the sequence is the organoaluminum-promoted Beckmann rearrangement of ketoxime derivatives, in which the organoaluminum compounds are used as amphiphilic reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary imino carbocation by the alkyl group that is originally attached to aluminum. The conventional process for accomplishing this transformation consists of the following steps: (i) Beckmann rearrangement of ketoxime or its derivative to lactam; (ii) conversion of the lactam to imino ether using trialkyloxonium tetrafluoroborate; (iii) alkylation of the imino ether with alkylolithium or Grignard reagent to produce imine, which requires a considerably longer time for execution.⁸

As oxime derivatives, oxime sulfonates can be used preferentially for the following reasons: (1) they are readily available from oximes using p-toluenesulfonyl chloride or methanesulfonyl chloride in the presence of base in almost quantitative yield; (2) they are easy to handle because of their fine crystalline properties; (3) they are sufficiently reactive to initiate the rearrangement by organoaluminum reagents.


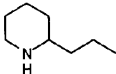


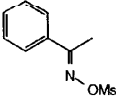
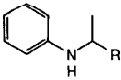
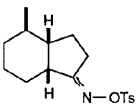
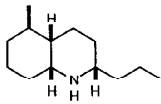
As shown in Table I, this reaction sequence has wide generality and is readily applicable to the straightforward synthesis of various naturally occurring alkaloids such as conine,⁹ pumiliotoxin C,¹⁰ and solenopsin A and B.¹¹ Oxime sulfonates of either linear or cyclic structures may be used. Obviously, the regioselectivity of the reaction follows the general rule of the Beckmann rearrangement,¹² and preferential migration of the group anti to the oxime sulfonate is observed. Diethylaluminum alkynides can be successfully used for the selective introduction of alkynyl groups to a substrate in preference to an ethyl group. Furthermore, the present procedure reduces the intermediate imine directly without isolation by using diisobutylaluminum hydride, thus excluding the troublesome isolation of unstable cyclic imino compound.

The organoaluminum-promoted Beckmann rearrangement-alkylation sequence represents a modern aspect of the classical Beckmann rearrangement, and has proved effective with other aluminum reagents of type R_2AlX ($X = SR, SeR, \text{ and } CN$) which would function in a similar way to trialkylaluminum compounds. Thus, a series of imino thioethers, selenoethers, and nitriles can be prepared with rigorous regioselectivity by using organoaluminum thiolates, selenolates, and cyanide, respectively.⁴

2-Propyl-1-azacycloheptane has been prepared by reduction of 2-aza-1-oxo-3-propylcycloheptane with lithium aluminum hydride,⁶ and from azacycloheptane by conversion to its formamidine, alkylation with 1-iodopropane, and subsequent hydrazinolysis.¹³

TABLE I

PREPARATION OF α -ALKYLATED AMINES FROM OXIME SULFONATES WITH
TRIALKYLALUMINUM - DIISOBUTYLALUMINUM HYDRIDE

Oxime Sulfonate (mp, °C)	Trialkylaluminum	Amine	Yield (%)
 (75-77)	Pr_3Al^a		55-58
 (43-45)	Me_3Al $\text{Et}_2\text{AlCl} \equiv \text{CBu}$		70 (R = Me) 67 (R = C \equiv CBu)
 (64-65)	Me_3Al $\text{Et}_2\text{AlCl} \equiv \text{CBu}$ $\text{Et}_2\text{AlCl} \equiv \text{CPh}$		67 (R = Me) 83 (R = C \equiv CBu) 67 (R = C \equiv CPh)
 (67-71)	Pr_3Al^b		60

Treatment with Pr_3Al at 40-80°C for 15-30 min.

Treatment with Pr_3Al at 25°C for 30 min.

1. Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Propyl-1-azacycloheptane: 1H-Azepine, hexahydro-2-propyl-, (\pm)- (11);
(85028-29-1)

Cyclohexanone oxime methanesulfonate: Cyclohexanone, O-(methanesulfonyl)oxime
(10); (80053-69-6)

Cyclohexanone oxime (8); Cyclohexanone, oxime (90: (100-64-1)

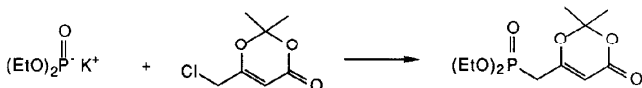
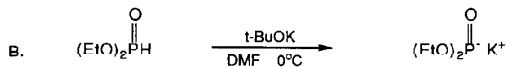
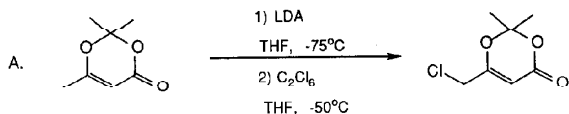
Methanesulfonyl chloride (8,9); (124-63-0)

Tripropylaluminum: Aluminum, tripropyl- (8,9); (102-67-0)

Diisobutylaluminum hydride: Aluminum, hydrodiisobutyl- (8); Aluminum,
hydro-bis(2-methylpropyl)- (9); (1191-15-7)

6-DIETHYLPHOSPHONOMETHYL-2,2-DIMETHYL-1,3-DIOXEN-4-ONE

(Phosphonic acid, [(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl])- ,
diethyl ester)



Submitted by Robert K. Boeckman, Jr., Robert B. Parni, James E. Macdonald,
and Anthony J. Thomas.¹

Checked by Stacey C. Slater and James D. White.

1. Procedure

A. *6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one*. A three-necked, 500 mL, round-bottomed flask is fitted with a nitrogen inlet, rubber septum, and a 125-mL dropping funnel. The flask is flame-dried, flushed with nitrogen and charged with diisopropylamine (22.0 mL, 0.16 mol) and 100 mL of tetrahydrofuran (THF) (Note 1). This solution is cooled in an ice bath, and the dropping funnel is charged with a solution of butyllithium (80.0 mL of a 1.88 M solution in hexane, 0.15 mol) which is added dropwise over 15 min (Note

2). The resulting solution is cooled to approximately -75°C in a dry ice-acetone bath and treated with a solution of 2,2,6-trimethyl-1,3-dioxen-4-one² (16.0 g, 0.11 mol) in tetrahydrofuran (20 mL) dropwise over 20 min (Note 3). During the addition, a fine yellow suspension forms. The enolate solution is stirred at -75°C for an additional 15 min and then transferred via cannula to a 1-L flask containing hexachloroethane³ (39.0 g, 0.16 mol) (Note 4) in tetrahydrofuran (150 mL) at -50°C to -55°C (dry ice-acetone bath) over 30 min. When the addition is complete, any residual enolate is transferred with an additional portion of tetrahydrofuran (20 mL). The resulting reaction mixture is allowed to warm slowly to -25°C over 30 min and poured into ice-cold aqueous 10% hydrochloric acid (200 mL), and the mixture is briefly shaken to discharge the red color. The organic layer is separated, and the aqueous layer is extracted with ether (2 x 100 mL). The combined organic extracts are washed with saturated aqueous sodium bicarbonate solution (100 mL), saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to afford 31.50-35.50 g of an oily solid. Column chromatography on Florisil (100-200 mesh, 400 g) (Note 5) and elution with hexane (1 L) and 20% ethyl acetate-hexane (2 L), gives 12.17-12.67 g (63-65%) of the desired product as a yellow oil (Notes 6, 7, and 8).

B. *6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one*. A 500-mL, three-necked flask is outfitted as above, flushed with nitrogen and charged with potassium tert-butoxide (21.0 g, 0.187 mol) and dimethylformamide (200 mL) (Note 9). The stirring mixture is cooled in an ice bath and treated with diethyl phosphite (26.7 g, 0.193 mol). The resulting solution is stirred in the ice bath for 20-40 min and then treated dropwise with a solution of 6-chloromethyl-2,2-dimethyl-1,3-dioxen-4-one (11.00 g, 0.062 mol) in tetrahydrofuran (50 mL) over 20 min. The resulting purple solution is stirred an

additional 15 min at 0°C and treated with concentrated hydrochloric acid dropwise until the purple color is discharged (approx. 6 mL). The resulting mixture is filtered by suction through Celite (Note 10), and the collected solids are washed with tetrahydrofuran (50 mL). The combined organic portions are treated with several grams of anhydrous potassium carbonate, filtered, and the tetrahydrofuran is removed with a rotary evaporator. Dimethylformamide and excess diethyl phosphite are removed by distillation at 0.4 mm with the bath temperature maintained below 50°C (Note 11). The residue is diluted with ethyl acetate (200 mL) and placed in the refrigerator at 0°C overnight. The solid which precipitates is removed by filtration, and the filtrate is concentrated under reduced pressure to ~ 75 mL and purified by flash chromatography (Notes 12 and 13) on 700 g of Florisil (9 x 22 cm column). Elution with 3 L of 1:1 ethyl acetate-hexane, 3 L of 3:1 ethyl acetate-hexane, and then 3 L of 100% ethyl acetate affords 8.30-8.56 g (48-50%) of 6-diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one (Notes 14 and 15). Mixed fractions may be rechromatographed to afford an additional 2-4% of product.

2. Notes

1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium benzophenone ketyl. Diisopropylamine was distilled under a nitrogen atmosphere from calcium hydride.

2. A solution of butyllithium in hexane (~ 1.8 M) was obtained from Lithcoa and standardized by titration against 2,5-dimethoxybenzyl alcohol.⁴

3. 2,2,6-Trimethyl-1,3-dioxen-4-one is commercially available from the Aldrich Chemical Company, Inc. and may be used without further purification.

4. Hexachloroethane was obtained from the Aldrich Chemical Company, Inc. and used without further purification.

5. Florisil is a magnesium silicate adsorbent obtained from the Floridin Company.

6. Substantial amounts of unreacted hexachloroethane may be recovered from early fractions.

7. The reaction may be carried out equally well on a 32-g scale.

8. The NMR and IR spectral data of the chloride are as follows: ^1H NMR (CDCl_3) δ : 1.74 (s, 6 H), 4.02 (s, 2 H), 5.53 (s, 1 H), IR (film) cm^{-1} : 2970, 1730, 1640, 1390, 1280, 1210, 1024.

9. Dimethylformamide (DMF) was distilled under reduced pressure (20 mm) from calcium hydride. Diethyl phosphite may be used directly from a freshly-opened bottle or redistilled before use.

10. This filtration is very slow, and a wide sintered-glass funnel is recommended.

11. The product phosphonate decomposes to diethylphosphonoacetone above 50°C , and care must be taken during the distillation and concentration of chromatography fractions that heating baths do not exceed this temperature.

12. The procedure of W. C. Still was utilized.⁵

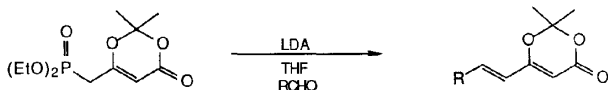
13. Chromatographic fractions were analyzed by TLC by elution with ethyl acetate, and were visualized with a permanganate spray. The phosphonate had $R_f = 0.35$.

14. The NMR and IR spectral data of the phosphonate are as follows: ^1H NMR (CDCl_3) δ : 1.37 (t, 6 H), 1.72 (s, 6 H), 2.81 (d, 2 H), 4.16 (m, 4 H), 5.40 (d, 1 H); IR (film) cm^{-1} : 2980, 1720, 1630, 1370, 1255. The absence of residual hexachloroethane was confirmed by ^{13}C NMR spectroscopy.

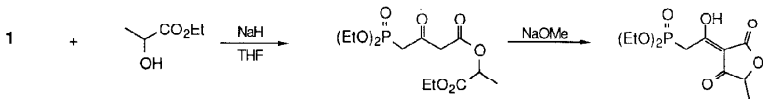
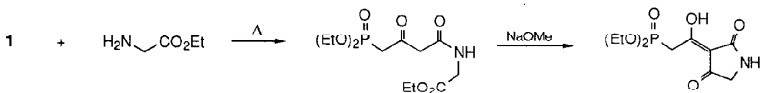
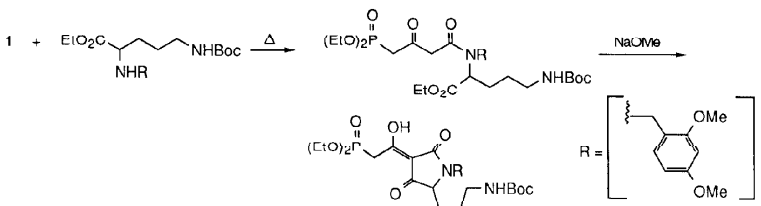
15. The phosphonate should be stored at 0°C. Under these conditions the purified product is stable for at least several months.

3. Discussion

This procedure is a modification of the previously-published procedure by Boeckman and Thomas.⁶ The acetone diketene adduct serves as a versatile, activated β -keto ester equivalent.^{2,3,7} Conversion of this material to the phosphonate by the procedure described above affords an even more versatile synthon which is useful for the preparation of protected analogues of the Nazarov reagents by means of a Wadsworth-Emmons olefination.^{8,9}

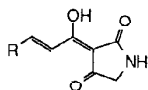


The title phosphonate and related substances undergo thermal decomposition to β -acyl ketenes at temperatures in excess of 50°C.¹⁰ Thus thermolysis in the presence of alcohols, amines, α -hydroxy esters, and α -amino esters affords the corresponding β -keto esters and amides; the latter two classes can be cyclized upon subsequent base treatment to unsaturated tetronic and tetramic acids and the related phosphonate reagents.^{6,11}



For sensitive amino acids prone to thermal dimerization to the related diketopiperazines, the reaction can be conducted in refluxing tetrahydrofuran solution in the presence of *p*-toluene- or camphorsulfonic acid as catalyst. Where possible the non acid-catalyzed thermal procedure is preferred since it generally provides cleaner products in higher yields.

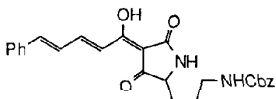
The resulting tetramic and tetronic acid phosphonate reagents undergo the Wadsworth-Emmons olefination⁹ with a variety of aldehydes to afford (*E*)- α,β -unsaturated and diene acyl tetramic and tetronic acids in good to excellent yields upon treatment with potassium *tert*-butoxide (2 equiv) in tetrahydrofuran. For readily enolizable substrates use of the *N*-protected systems is generally required. The following compounds have been prepared, in the indicated yields, in this manner:



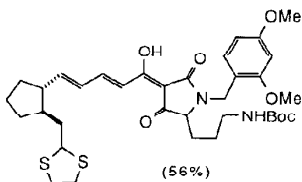
R = Ph (75%)

R = t-Bu (73%)

R =  (63%)



(71%)



(56%)

Two alternative methods for the preparation of phosphorus-activated tetramic acid reagents have recently been described.¹² These reagents have served to provide a workable solution to the problem of construction of the dienoyl tetramic acid unit required for the synthesis of Urandamycin-A.¹³⁻¹⁶

1. Department of Chemistry, University of Rochester, Rochester, NY 14627.
2. Carroll, M. F.; Bader, A. R. *J. Am. Chem. Soc.* **1953**, *75*, 5400.
3. (a) Gronowitz, S.; Hornfeldt, A. B.; Pettersson, K. *Synth. Commun.* **1973**, *3*, 213; (b) Kattenberg, J.; de Waard, E. R.; Huisman, H. O. *Tetrahedron* **1973**, *29*, 4149; (c) Smith, A. B., III; Scarborough, Jr., R. M. *Tetrahedron Lett.* **1978**, 4193.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one: Phosphonic acid, [(2,2-dimethyl 4 oxo 4H-1,3-dioxin-6-yl)methyl]-, diethyl ester (11); (81956-28-7)

6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one: 4H-1,3-Dioxin-4-one, 6-(chloromethyl)-2,2-dimethyl- (11); (81956-31-2)

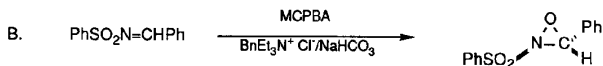
2,2,6-Trimethyl-1,3-dioxen-4-one: m-Dioxin-4-one, 2,2,6-trimethyl- (8,9); (5394-63-8)

Hexachloroethane: Ethane, hexachloro- (8,9); (67-72-1)

Diethyl phosphite: Phosphonic, acid, diethyl ester (8,9); (762-04-9)

(±)-trans-2-(PHENYLSULFONYL)-3-PHENYLOXAZIRIDINE

(Oxaziridine, 3-phenyl-2-(phenylsulfonyl)-)



Submitted by Lal C. Vishwakarma, Orum D. Stringer, and Franklin A. Davis.¹

Checked by James Pribish and Edwin Vedejs.

1. Procedure

A. *N*-Benzylidenebenzeneulfonamide. A 3-L, one-necked, round-bottomed flask is equipped with a mechanical stirrer (Note 1), Dean-Stark water separator (Note 2), double-walled condenser attached to an argon gas inlet and outlet needle connectors through a mineral oil bubbler. Into the flask are placed 150 g of 5 Å powdered molecular sieves (Note 3), 2.0 g of Amberlyst 15 ion exchange resin (Note 4), 157 g of benzenesulfonamide (Note 5), 1650 mL of dry toluene and 107.5 g (1.014 mol) of freshly-distilled benzaldehyde (Note 5). The reaction mixture is stirred and heated at reflux under an argon atmosphere. Water which separates during the reaction is periodically removed and refluxing is continued until water separation ceases (approximately 16 hr). The reaction mixture is cooled to room temperature without stirring and the insoluble materials are filtered through a 500-mL capacity sintered-glass funnel of medium porosity. The residue in the filter funnel is washed thoroughly with another 700 mL of toluene in three portions. The collected

filtrate is concentrated with a rotary evaporator to give a thick yellow oily residue which usually solidifies on standing. The residue is triturated with 800 mL of distilled pentane and the solid is broken into a powder with the aid of a flat-ended glass rod. The solid is separated by filtration through a 500-mL sintered glass funnel of medium porosity, washed with distilled pentane (2 x 100 mL) and air dried. The yield is 212 g (97%); mp 76-80°C (Note 6).

Although of sufficient purity for the next step, the sulfonylimine can be further purified by recrystallization. In a 2-L Erlenmeyer flask containing 150 mL of ethyl acetate is dissolved, with warming, 212 g of the crude sulfonylimine. After the mixture is cooled to room temperature, about 400 mL of pentane is added and the solution is allowed to stand at room temperature for 2-3 hr. The colorless crystalline product is collected by filtration, washed with 100 mL of pentane and air dried to give 191.5 g (78%), mp 78-80°C. The washings and filtrate are combined and the volume reduced by about one third using a rotary evaporator. A second crop of crystals, 20.2 g (8%), mp 75-79°C, was obtained on standing for several hours.

B. *(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine*. A 5-L, three-necked flask is equipped with a mechanical stirrer and a 500-mL pressure-equalizing addition funnel. Into the flask are placed 500 mL of saturated aqueous sodium bicarbonate solution, 12.5 g (0.055 mol) of benzyltriethylammonium chloride (BTEAC) and 122.5 g (0.50 mol) of N-benzylidenebenzenesulfonamide dissolved in 380 mL of chloroform (Note 7). The reaction mixture is stirred vigorously at 0-5°C in an ice bath while a solution of 111.6 g (0.55 mol) of 85% m-chloroperoxybenzoic acid (MCPBA) dissolved in 1000 mL of chloroform is added dropwise. After the addition of the peracid, which takes about 1 hr, the reaction mixture is stirred for an additional hour at this temperature. A 3-L separatory funnel is used to separate the chloroform

solution and wash it successively with 600 mL of cold water, 600 mL of aqueous 10% sodium sulfite, water (2 x 600 mL) and 250 mL of a saturated sodium chloride solution (Note 8). After the chloroform solution is dried over anhydrous potassium carbonate for 2 hr (Note 9), it is filtered and solvent is removed with a rotary evaporator, keeping the water bath temperature below 40°C. The resulting white solid residue is washed with a small portion of pentane, dissolved in a minimum of ethyl acetate (about 700-800 mL) without heating, and filtered through fluted filter paper; 400 mL of pentane is added to the filtrate. After the white crystalline oxaziridine is cooled in the refrigerator overnight, it is separated by filtration, transferred to a 500-mL Erlenmeyer flask, washed with 200 mL of pentane, filtered and air dried for 1 hr. The yield is 83.5 g; mp 92-94°C. The mother liquor is reduced to about 300 mL and cooled in the refrigerator to give 36.6 g of a light yellow solid; mp 87-90°C. This second crop is placed in a 250-mL Erlenmeyer flask and triturated with 50 mL of anhydrous ether followed by the addition of 60 mL of pentane. The oxaziridine is isolated by filtration to give 31.1 g; mp 94-95°C (dec) (Note 10, 11). The combined yield is 114.6 g (88%).

The 2-sulfonyloxaziridine can be stored in a brown bottle in the refrigerator. Storage at room temperature is potentially hazardous (Note 12).

2. Notes

1. A Teflon-coated, heavy duty, oval-shaped spin bar was used by the submitters for efficient stirring.

2. A Dean-Stark water separator equipped with a Teflon stopcock for water removal was used.

3. Linde powdered 5 Å molecular sieves were used as obtained from the supplier.

4. Amberlyst 15 ion-exchange resin is a strongly acidic, macroreticular resin purchased from Aldrich Chemical Company, Inc. The reaction fails in the absence of the acid catalysts.

5. Benzenesulfonamide, m-chloroperoxybenzoic acid and benzaldehyde were obtained from the Aldrich Chemical Company, Inc. and, with the exception of the latter, used without additional purification.

6. The ^1H NMR spectrum of N-benzylidenebenzenesulfonamide is as follows: (CDCl_3) δ : 7.6 (m, 6 H), 8.0 (m, 4 H) and 9.05 (s, 1 H).

7. Analytical reagent grade chloroform, Fisher Scientific Company, was used as obtained.

8. It is necessary to wash with a 10% NaHCO_3 solution, before the sodium chloride wash, if a large excess of m-chloroperoxybenzoic acid is used.

9. If the solution is dried for long times over potassium carbonate, decomposition of the oxaziridine sometimes occurs.

10. The ^1H NMR spectrum of trans-2-(phenylsulfonyl)-3-phenyloxaziridine is as follows: (CDCl_3) δ : 5.5 (s, 1 H), 7.4 (s, 5 H) and 7.6-7.8 (m, 3 H) and 8.05 (br d, 2 H, $J = 7.1$).

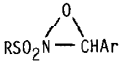
11. Careful recrystallization from ethyl acetate (saturated solution at 25°C ; cool to -20°C) gave colorless crystals, ca. 20% recovery, mp $95-95.5^\circ\text{C}$.

12. Exothermic decomposition of a 500-g quantity after 2 weeks storage at room temperature is reported by Dr. G. C. Crockett, the Aldrich Chemical Company, Inc. Sufficient force was generated to shatter the container and char the oxaziridine.

3. Discussion

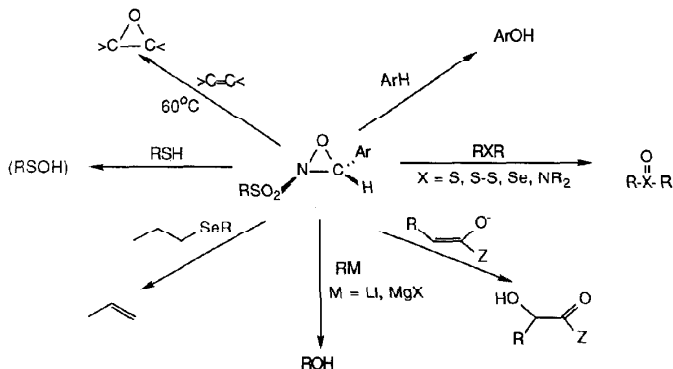
This procedure is representative of a general procedure, for the synthesis of trans-2-sulfonyloxaziridines previously reported on a small scale (Table I).^{2a} trans-2-(Phenylsulfonyl)-3-(p-nitrophenyl)oxaziridine was prepared on a 0.16-molar scale in greater than 85% yield. The Baeyer-Villiger type oxidation of the sulfonimine affords only the trans-oxaziridine. The synthesis of the sulfonimine ($\text{PhSO}_2\text{N}=\text{CHPh}$) directly from the sulfonamide and aromatic aldehyde is described here. This modification avoids use of the intermediate diethyl acetal used in earlier preparations of these compounds.²

TABLE I
PREPARATION OF 2-SULFONYLOXAZIRIDINES^{2a,b}

	% Yield	mp (°C, dec.)
R=Ph, Ar=3-NO ₂ Ph	83	113-5
R=Ph, Ar=4-NO ₂ Ph	80	134-6
R=Me, Ar=Ph	85	59-61
R=PhCH ₂ , Ar=Ph	90	118-9

2-Sulfonyloxaziridines are useful aprotic and neutral oxidizing reagents which, in general, afford greater selectivity for oxidations than do peracids. 2-Sulfonyloxaziridines have been employed in the oxidation of sulfides to sulfoxides,³ disulfides to thiosulfates,³ selenides to selenoxides,⁴ thiols to sulfenic acids (RSOH),⁵ organometallic reagents to alcohols and phenols,⁶ ketone and ester enolates to α -hydroxy carbonyl compounds,⁷ in the epoxidation of alkenes,⁸ and in the conversion of chiral amide enolates to optically active α -hydroxy carboxylic acids (93-99% ee).^{9,10} These reagents can be used in the study of reactive oxidation intermediates and for mechanistic studies of oxygen-transfer reactions because of the ease with which the course of the oxidation can be monitored by proton NMR.

Oxygen-Transfer Reactions of 2-Sulfonyloxaziridines



Oxidation of chiral sulfonimines ($R^*SO_2N=CHAR$)¹¹ and chiral sulfamyl-imines ($R^*RNSO_2N=CHAR$)¹² affords optically active 2-sulfonyloxaziridines and 2-sulfamylloxaziridines, respectively. These chiral, oxidizing reagents have been used in the asymmetric oxidation of sulfides to sulfoxides (15-68% ee),¹¹⁻¹³ selenides to selenoxides (8-9% ee),¹⁴ enolates to α -hydroxycarbonyl compounds (8-37% ee)¹⁵ and in the asymmetric epoxidation of alkenes (15-40% ee).¹⁶

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

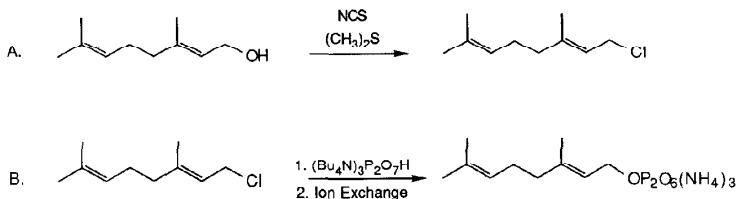
(±)-2-(Phenylsulfonyl)-3-phenyloxaziridine: Oxaziridine, 3-phenyl-2-(phenylsulfonyl)- (10); (63160-13-4)

N-Benzylidenebenzenesulfonamide: Benzenesulfonamide, N-benzylidene- (8);

Benzenesulfonamide, N-(phenylmethylene)- (9); (13909-34-7)

TRISAMMONIUM GERANYL DIPHOSPHATE

(Diphosphoric acid, mono(3,7-dimethyl-2,6-octadienyl) ester
(E)-, trisammonium salt)



Submitted by Andrew B. Woodside, Zheng Huang, and C. Dale Poulter.¹

Checked by Pamela Seaton and James D. White.

1. Procedure

A. *Geranyl chloride.* To a flame-dried, 100-mL, three necked, round-bottomed flask equipped with a magnetic stirrer, low temperature thermometer, rubber septum, and nitrogen inlet adapter, is added 1.47 g (11 mmol) of N-chlorosuccinimide (Note 1). The powder is dissolved in 45 mL of dry dichloromethane (Note 2), and the resulting solution is cooled to -30°C with a dry ice/acetonitrile bath. Freshly distilled dimethyl sulfide (0.87 mL, 0.74 g, 12 mmol) is added dropwise by syringe. The mixture is warmed to 0°C with an ice-water bath, maintained at that temperature for 5 min, and cooled to -40°C . To the resulting milky white suspension is added dropwise by syringe 1.54 g (10 mmol) of geraniol (Note 3) dissolved in 5 mL of dry dichloromethane. The suspension is warmed to 0°C with an ice-water bath and stirred for 2 hr. The ice bath is then removed, and the reaction mixture is

allowed to warm to room temperature. Stirring is continued for an additional 15 min. The resulting clear, colorless solution is poured into a 250-mL separatory funnel and washed with 25 mL of saturated sodium chloride. The aqueous layer is washed with two 20-mL portions of pentane. The pentane extracts and an additional 20-mL portion of pentane are added to the methylene chloride extract. The resulting solution is washed twice with 10 mL of saturated sodium chloride and dried over magnesium sulfate. Solid material is removed by vacuum filtration through a fritted glass funnel, and most of the solvent is removed with a rotary evaporator at aspiratory pressure. The last traces of solvent are removed by pumping at high vacuum (0.2 mm) for 1.5 hr. The resulting pale yellow oil (1.61 g, 9.3 mmol, 93%) is used directly in the next step (Note 4).

B. *Trisammonium geranyl diphosphate*. To a flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet adapter is added 9.14 g (9.3 mmol) of tris(tetrabutylammonium) hydrogen pyrophosphate trihydrate (Note 5). The flocculant white solid is dissolved in 20 mL of dry acetonitrile (Note 6). To the resulting milky white suspension (Note 7) is added 0.83 g (4.8 mmol) of geranyl chloride. The mixture is allowed to stir at room temperature for 2 hr. Solvent is then removed with a rotary evaporator using a 40°C water bath. The pale yellow residue is dissolved in 3 mL of ion exchange buffer (Note 8), and the resulting clear solution is loaded onto a 4 x 15-cm column of Dowex AG 50W-X8 (100-200 mesh) cation exchange resin (ammonium form) (Note 9). The flask is washed twice with 5 mL of buffer and both washes are loaded onto the column before elution with 360 mL (two column volumes) of ion exchange buffer (Note 10). The eluant is collected in a 500-mL freeze-drying flask, frozen as described in Note 5, and lyophilized for 18-24 hr (Note 11) to yield 2.57 g of a white solid. The material is dissolved

in 5 mL of 0.05 M ammonium bicarbonate, and the clear solution is transferred to a 50-mL centrifuge tube. Twenty milliliters of 1:1 (v/v) acetonitrile:isopropyl alcohol is added, and the contents are mixed thoroughly on a vortex mixer, during which time a white precipitate forms. The suspension is cleared by centrifugation for 5 min at 2000 rpm. The supernatant solution is removed with a pipette, the residue is suspended in 5 mL of 0.05 M ammonium bicarbonate, and the process is repeated. Three additional extractions are performed using 2 mL of 0.05 M ammonium bicarbonate and 8 mL of acetonitrile:isopropyl alcohol. The combined supernatant solutions (approximately 80 mL) are concentrated to approximately 5 mL with a rotary evaporator at 40°C (Note 12).

One half of the concentrated extract, dissolved in an equal volume of chromatography buffer (Note 13), is loaded onto a 5.5 x 18-cm cellulose flash column² (Note 14). The flask is rinsed with three 5-mL portions of chromatography buffer and each is loaded onto the column. The column is then eluted with 900 mL of chromatography buffer. After a 50-mL forerun, twenty-eight 30-mL fractions are collected, and every second fraction is analyzed by thin layer chromatography (Note 15). Fractions containing trisammonium geranyl diphosphate (typically 12-23) are pooled and concentrated to approximately 120 mL with a rotary evaporator at 40°C. The concentrate is transferred to a 250-mL freeze-drying flask and lyophilized for 18-24 hr as previously described in Note 5. The resulting flocculant white solid is collected and stored at -78°C. The cellulose chromatography is repeated to yield a total of 1.51-1.55 g (85-87%) of trisammonium geranyl diphosphate from geraniol (Note 16).

2. Notes

1. N-Chlorosuccinimide (from the Aldrich Chemical Company, Inc.) is recrystallized from benzene (*CAUTION: CARCINOGENIC*).

2. Methylene chloride is distilled from phosphorus pentoxide immediately before use.

3. Geraniol (from the Aldrich Chemical Company, Inc.) is distilled before use, bp 90-92°C at 3 mm.

4. The IR, ^1H NMR, and ^{13}C NMR spectra of this material are identical with those for distilled geranyl chloride (bp 49-51°C at 0.2 mm). Distillation on a small scale significantly reduces the yield, and there is no improvement in the yield of the phosphorylation reaction using distilled material. A synthesis of geranyl chloride was reported earlier in this series.³ We find, however, that the procedure of Corey, Kim, and Takeda⁴ is more convenient.

5. Disodium dihydrogen pyrophosphate (3.13 g, 14 mmol) (from Sigma Chemical Co.) is dissolved in 25 mL of deionized water containing 1 mL of concentrated ammonium hydroxide. The resulting clear solution is loaded onto a 2 x 30-cm column of Dowex AG 50W-X8 cation exchange resin (100-200 mesh, H^+) and eluted with deionized water. The first 150 mL of eluant is collected in a 250-mL freeze-drying flask. A magnetic stirring bar is added, and the solution is titrated to pH 7.3 by slow addition of tetrabutylammonium hydroxide (Aldrich Chemical Company, Inc.). The stirring bar is removed, and the flask is placed in a dry ice/propanol bath. The flask is spun slowly in a manner to uniformly freeze its contents to the walls. Water is removed by lyophilization for 24 hr. The resulting flocculant white solid (10.6 g, 83%) contains 3 to 4 waters of hydration and is used without further purification. The

material is extremely hygroscopic and can be stored in a desiccator over phosphorus pentoxide.

6. Reagent grade acetonitrile is distilled from phosphorus pentoxide immediately before use.

7. Clear solutions can be obtained by filtration. Residual water can be removed from freeze-dried salt by repeated evaporation of dry acetonitrile (rotary evaporator). This material is not noticeably more effective than the salt obtained after lyophilization.

8. Ammonium bicarbonate (2.0 g) is dissolved in 1 L of 2% (v/v) isopropyl alcohol/water. The resulting solution is 25 mM in ammonium bicarbonate.

9. The ammonium form of the resin is generated by placing 188 mL of Dowex AG 50W-X8 (100-200 mesh, H^+ form) in an 1-L feitted glass funnel and washing the material with four 200-mL portions of concentrated ammonium hydroxide. The resin is washed with 200-mL portions of deionized water until the pH of the filtrate drops to pH 7, then with two 200-mL portions of ion exchange buffer. The washed resin is suspended in 200 mL of buffer and slurry-packed into the column.

10. Dowex AG 50W-X8 (100-200 mesh) from BioRad has a capacity of 1.7 meq per mL of resin bed. This represents approximately a 10-fold excess of exchangeable ions in the resin over material loaded onto the column. However, the tetrabutylammonium cation has a lower affinity for the resin than the ammonium cation. To optimize the exchange, it is important to maintain a low concentration of ammonium ion in the exchange buffer, to elute the material slowly (less than 9 mL/min on the 4 x 15-cm column), and to elute with only two column volumes of exchange buffer; otherwise previously exchanged tetrabutylammonium cation will begin to elute from the column. Incomplete exchange

dramatically reduces the efficiency of the subsequent purification on cellulose. The efficiency of the exchange can be determined by ^1H NMR.

11. Trisammonium geranyl diphosphate will decompose if left under vacuum for extended periods. It is important to remove the sample from the freeze-drier within a few hours after water has been removed.

12. This material is stored at -20°C until chromatography on cellulose.

13. Chromatography buffer is prepared by dissolving 4.0 g of ammonium bicarbonate in 250 mL of deionized water and adding 500 mL of isopropyl alcohol and 250 mL of acetonitrile. The resulting solution is approximately 50 mM in ammonium bicarbonate.

14. Whatman CF11 fibrous cellulose powder is prepared for chromatography by the following procedure. Cellulose powder (1 L, dry volume) is mixed with 700 mL of deionized water in a 2-L beaker by vigorous stirring with a glass rod. The suspension is allowed to stand for 30 min, and the water is removed by decantation. The same procedure is followed as the cellulose is washed in succession with two 700-mL portions of 0.1 N hydrochloric acid, two 700-mL portions of deionized water, two 700-mL portions of 0.1 N sodium hydroxide, two 700-mL portions of deionized water, and two 700-mL portions of 1:1 (v/v) isopropyl alcohol:water. The material is stored at 4°C in 1:1 isopropyl alcohol:water until used. The column is slurry-packed in 1:1 isopropyl alcohol:water and washed with 1.3 L (approximately three column volumes) of acetonitrile. The column is then washed with 1.3 L of 1:1 isopropyl alcohol:water and equilibrated with 1.3 L of chromatography buffer (Note 13).

15. E. Merck cellulose thin-layer chromatography plates (available from American Scientific Products) are developed with chromatography buffer (Note 13) and visualized with sulfosalicylic acid/ferric chloride spray.⁵ The system consists of a solution of 1.0 g of sulfosalicylic acid (from Aldrich

Chemical Co., Inc.) dissolved in 100 mL of 3:2 (v/v) ethanol:water and a solution of 0.20 g of ferric chloride in 100 mL of 4:1 (v/v) ethanol:water. Plates are first sprayed with the sulfosalicylic acid solution (thoroughly wetted but not dripping) and allowed to air dry. The ferric chloride solution is lightly sprayed onto the plates. Phosphate-containing compounds appear as white spots on a pink background. A second light spraying with ferric chloride may be necessary to make the spots pronounced. It is *important* to prepare both sprays freshly. Their shelf life is only about 6 hr. Under these conditions the trisammonium geranyl diphosphate has an R_f of 0.35. Residual tetrabutylammonium salt moves with the solvent front, and ammonium inorganic pyrophosphate remains at the origin.

16. This material migrates as a single spot on the cellulose thin-layer system and has no extraneous peaks in the ^1H , ^{13}C , and ^{31}P NMR spectra. The IR and NMR spectral properties of trisammonium geranyl diphosphate are as follows. IR (KBr) cm^{-1} : 3100-3500 (br), 2000,2900 (br), 1650, 1450, 1400, 1200, 1120, 1080, 1015, and 900; ^1H NMR (300 MHz, $\text{D}_2\text{O}/\text{ND}_4\text{OD}$) δ : 1.62 (s, 3 H, methy), 1.68 (s, 3 H, methyl) 1.72 (s, 3 H, methyl), 2.11 (m, 4 H, CH_2 at C_4 and C_5), 4.47 (t, 2 H, $J_{^1\text{H}, ^1\text{H}} = 6.5$, $J_{^1\text{H}, ^{31}\text{P}} = 6.5$, CH_2 at C_1), 5.22 (broad, 1 H, $J_{^1\text{H}, ^1\text{H}} = 6.5$, H at C_6), and 5.47 (t, 1 H, $J_{^1\text{H}, ^1\text{H}} = 6.5$, H at C_2); ^{13}C NMR (75 MHz, $\text{D}_2\text{O}/\text{ND}_4\text{OD}$, ^1H decoupled): 18.28 (CH_3), 19.69 (CH_3), 27.55 (CH_3), 28.60 (CH_2), 41.55 (CH_2), 65.42 (CH_2 , d, $J_{^{13}\text{C}, ^{31}\text{P}} = 4.0$), 122.85 (CH, d, $J_{^{13}\text{C}, ^{31}\text{P}} = 7.5$), 127.10 (CH), 136.68 (C), and 145.76 (C); ^{31}P NMR (32 MHz, $\text{D}_2\text{O}/\text{ND}_4\text{OD}$, ^1H decoupled): -11.23 (d, 1 P, $J_{^{31}\text{P}, ^{31}\text{P}} = 20$) and -9.10 (d, 1 P, P_2).

3. Discussion

Previous methods for the preparation of salts of geranyl diphosphate and other allylic isoprenoid diphosphates are based on condensation between the alcohol and inorganic phosphate by trichloroacetonitrile as originally reported by Cramer⁶ and modified by Popjak.⁷ The reaction generates a complex mixture of organic and inorganic polyphosphates which must be separated by chromatography. The desired diphosphate ester has been prepared on small scales in yields of up to 30%,⁸ but in our experience, the yields of pure material obtained by this procedure are usually less than 10%.

The direct displacement reaction can be used to prepare many of the common diphosphate esters in the isoprene biosynthetic pathway,⁹ including isopentenyl diphosphate.^{10,11} The yields are typically 60-90% from the alcohol, and the absence of phosphate polymers found in the Cramer procedure simplifies the purification step. We have also used the displacement procedure to prepare radio-labeled material for biosynthetic studies.¹²

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

Geranyl chloride: 2,6-Octadiene, 1-chloro-3,7-dimethyl-, (E)- (8.9);
(5389-87-7)

N-Chlorosuccinimide: Succinimide, N-chloro- (8); 2,5-Pyrrolidinedione,
1-chloro- (9); (128-09-6)

Geraniol: 2,6-Octadien-1-ol, 3,7-dimethyl-, (E)- (9); (106-24-1)

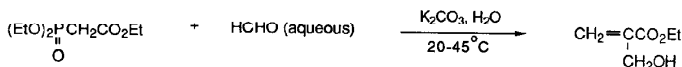
Tris(tetrabutylammonium) hydrogen pyrophosphate: 1-Butanaminium, N,N,N-
tributyl-, diphosphate (3:1) (10); (76947-02-9)

Disodium dihydrogen pyrophosphate: Pyrophosphoric acid, disodium salt (8);
Diphosphoric acid, disodium salt (9); (7758-16-9)

Tetrabutylammonium hydroxide: Ammonium tetrabutyl-, hydroxide (8); 1-
Butanaminium, N,N,N-tributyl-, hydroxide (9); (2052-49-5)

ETHYL α -(HYDROXYMETHYL)ACRYLATE

(2-Propenoic acid, 2-(hydroxymethyl)-, ethyl ester)



Submitted by J. Villieras and M. Rambaud.¹

Checked by Christina M. J. Fox and James D. White.

1. Procedure

A. *Ethyl α -(hydroxymethyl)acrylate*, (Note 1). A 1000-mL, four-necked, round-bottomed flask is fitted with a mechanical stirrer, 250-mL pressure-equalizing funnel, condenser, and thermometer. Paraformaldehyde (48 g, 1.6 mol), 1 N phosphoric acid (4 mL) and water (110 mL) are heated at 90°C for 1.5 hr to form a clear aqueous formaldehyde solution. This solution is cooled to room temperature. Triethyl phosphonoacetate (89.6 g, 0.4 mol) is added to the flask and the solution is stirred at room temperature at 1000 rpm. A solution of potassium carbonate (60.7 g, 0.44 mol) in water (60 mL) is added at room temperature (first slowly: 10 mL in 10 min) and then more rapidly (40 min). The temperature reaches 35-40°C and must be maintained at this level (with a water bath if necessary). Stirring is continued for 5 min at 40°C after the end of the addition; then the mixture (liquid-liquid heterogenous mixture) must be cooled rapidly to room temperature using an ice bath (Note 2) while diethyl ether (200 mL) and brine (150 mL) are added. After decantation, the mixture is extracted with ether (three 100-mL portions). The combined organic layers are washed with brine (two 100-mL portions) (Note 3) and dried over magnesium sulfate; the solvents are evaporated under reduced pressure and the

remaining oil is distilled to give a fraction at 65-70°C (1 mm) which weighs 38.5-41.6 g (74-80%), n_D^{20} 1.4494. The hydroxy ester is of high purity as shown by GLC analysis (25 m silica capillary OV-1 column) and spectral data (Notes 4, 5).

2. Notes

1. All manipulations should be carried out in a well-ventilated hood. The preparation requires the use of formaldehyde solution, and gives rise to ethyl acrylate as a secondary product, the amount of which increases if the addition of the carbonate solution is too rapid and the temperature rises to 45°C.

A freshly-opened supply of paraformaldehyde purchased from Aldrich Chemical Company, Inc. was used by the checkers. The use of commercial formaldehyde solutions which now contain up to 15% methanol leads to the formation of several by-products which cannot be separated by distillation from the α -(hydroxymethyl)acrylate.

2. This experimental procedure must be followed carefully to avoid partial decomposition of ethyl α -(hydroxymethyl)acrylate. The reaction is stopped rapidly after the addition of the carbonate solution (5 min) to prevent formation of high molecular weight by-products which result from transesterification and Michael addition, both of which occur in the basic medium. However, about 25% of the product is lost. Addition of diethyl ether during cooling minimizes side reactions.

3. Treatment with brine allows total elimination of base in the organic layer and prevents any side reaction during the distillation.

4. The spectral properties of ethyl α -(hydroxymethyl)acrylate are as follows: ^1H NMR (CCl_4) δ : 4.20 (2 H, $\text{CH}_2\text{-OH}$); 5.80 and 6.15 (2 H, $\text{CH}_2\text{=}$); ^{13}C NMR (CDCl_3) δ : 60.9 (CH_2OH); 124.8 ($\text{CH}_2\text{=C}$); 140.2 ($\text{CH}_2\text{=C}$); 166.5 (COOEt).

5. α -(Bromomethyl)-, α -(chloromethyl)-, α -(iodomethyl)-, and α -(fluoromethyl)acrylates are easily obtained from the α -(hydroxymethyl)acrylate² as illustrated in the following procedure.

A 500-mL, four-necked, round-bottomed flask is fitted with a mechanical stirrer, 100-mL pressure-equalizing addition funnel, reflux condenser capped with a drying tube (silica gel) and a thermometer (-90°C to $+60^\circ\text{C}$). The flask is charged with a stirred solution of ethyl α -(hydroxymethyl)acrylate (33.84 g, 0.26 mol) in dry ether (250 mL) at -10°C . Phosphorus tribromide (34 g, 11.5 mL, 0.12 mol) is added slowly (15 min). The temperature is allowed to rise to 20°C and stirring is continued for 3 hr. Water (150 mL) is added at -10°C and the mixture is extracted with technical-grade hexane (three 50-mL portions). The organic phase is washed twice with a saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. The solvents are removed with a rotary evaporator under reduced pressure, and the remaining oil is distilled to give ethyl α -(bromomethyl)acrylate, bp $85\text{--}87^\circ\text{C}$ (20 mm) which weighs 43.8 g (87%), n_D^{20} 1.4502. The ester is of high purity as shown by GLC analysis on a capillary OV-1 column, and spectral data.

The spectral properties of ethyl α -(bromomethyl)acrylate are as follows: ^1H NMR (CCl_4) δ : 4.15 (2 H, CH_2Br); 5.90 and 6.22 (2 H, $\text{H}_2\text{C=}$); ^{13}C NMR (CDCl_3) δ : 29.2 (CH_2Br), 126.5 ($\text{CH}_2\text{=C}$); 137.8 ($\text{CH}_2\text{=C}$); 164.5 (COOEt).

3. Discussion

Ethyl α -(hydroxymethyl)acrylate can be used for the synthesis of chloro and bromomethyl acrylates. The fluoro and iodo compounds have been prepared easily by halogen exchange from ethyl α -(bromomethyl)acrylate.²

The same procedure can be applied to the synthesis of diethyl α -(bromomethyl)vinylphosphonate.^{3,4} The keto analogs can be obtained in the same way.⁵

The procedure described here is relatively new and gives improved overall yields of 60-67% for the preparation of ethyl α -(bromomethyl)acrylate in two stages from commercially available starting materials. Other more complex and less productive procedures have been described.⁶

Ethyl α -(bromomethyl)acrylate has been used extensively for the synthesis of α -methylene lactones from ketones and aldehydes,⁷ and α -methylene lactams, which are known for their cytotoxic activity,⁷⁻⁹ from imines.⁸

1. Laboratoire de Synthèse Organique Sélective, associé au C.N.R.S. n°475, Faculté des Sciences, 2. rue de la Houssinière, F-44072 Nantes, France.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Ethyl α -(hydroxymethyl)acrylate: 2-Propenoic acid, 2-(hydroxymethyl)-, ethyl ester (9); (10029-04-6)

Triethyl phosphonoacetate: Acetic acid, phosphono-, triethyl ester (8);

Acetic acid, (diethoxyphosphinyl)-, ethyl ester (9); (867-13-0)

Ethyl α -(bromomethyl)acrylate: Acrylic acid, 2-(bromomethyl)-, ethyl ester (8); 2-Propenoic acid, 2-(bromomethyl)-, ethyl ester (9); (17435-72-2)

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- 2426 Vicinal Dicarboxylation of an Alkene: *cis*-1-Methylcyclohexane-1,2-dicarboxylic Acid
J.-P. Deprés and A. E. Greene, LEDSS, Université Scientifique et Médicale de Grenoble, BP 68, F-38402 Saint Martin d'Heres Cedex, France
- 2436 Methyl 2-Chloro-2-cyclopropylideneacetate
T. Liese, F. Seyed-Mahdavi, and A. de Meijere, Inst. für Organische Chemie und Biochemie, Universität Hamburg, Martin-Luther-King-Platz 6, 2000 Hamburg 13, Germany
- 2437 1-Chloro-1-(trichloroethenyl)cyclopropane
T. Liese, F. Jaekel, and A. de Meijere, Inst. für Organische Chemie und Biochemie, Universität Hamburg, Martin-Luther-King-Platz 6, 2000 Hamburg 13, Germany
- 2448* Palladium(0)-Catalyzed Syn-1,4-Addition of Carboxylic Acids to Cyclopentadiene Monoepoxide: *Cis*-3-Acetoxy-5-Hydroxycyclopent-1-ene
D. R. Deardorff and D. C. Myles, Department of Chemistry, Occidental College, Los Angeles, CA 90041
- 2449 Methyl 7-Hydroxyhept-5-ynoate
G. Casy, J. W. Patterson and R. J. K. Taylor, School of Chemical Science, University of East Anglia, Norwich, NR4 7TJ, United Kingdom
- 2450* R-(+)-1,1'-Binaphthalene-2,2'-diol
L. K. Truesdale and D. L. Coffen, Research Department, Hoffmann-La Roche Inc., Nutley, NJ 07110
- 2452 Selective Paraffin Hydroxylations with Activated Peroxycarboxylic Acids: 7aH-*cis*-3a-Hydroxy Tetrahydroindene
H.-J. Schneider, W. Müller and N. Nguyen-Ba, Fachrichtung Organische Chemie der Universität des Saarlandes, D-6600 Saarbrücken 11, West Germany
- 2453* The Carroll Rearrangement: Synthesis of 5-Dodecen-2-one
S. R. Wilson and C. E. Augelli, Department of Chemistry, New York University, New York, NY 10003
- 2455* Preparation of 1,4-Di-O-Alkyl Threitol from Tartaric Acid: 1,4-Di-O-Benzyl-L-Threitol
E. A. Mash, K. A. Nelson, S. Van Deusen, and S. B. Hemperly, Department of Chemistry, The University of Arizona, Tucson, AZ 85721
- 2457 Enantioselective Oxidation of Sulfides: Synthesis of (-)-(S)-Methyl *p*-Tolyl Sulfoxide
S. H. Zhao, O. Samuel, and H. B. Kagan, Laboratoire de Synthèse Asymétrique, Université Paris-Sud, 91405 Orsay, France

- 2461 Conversion of 3-Phenylpropene to 1-Bromo-3-phenyl-2-propanone
T. Kageyama, Y. Tobito, A. Katoh, Y. Ueno, and M. Okawara,
Department of Industrial Chemistry, Faculty of Engineering,
Kanto-Gakuin University, Mutsuura, Yokohama 236, Japan
- 2466 Preparation and Use of Lithium Acetylide: 1-Methyl-2-Ethynyl-endo-
3,3-Dimethyl-2-Norbornanol
M. M. Midland, J. I. McLoughlin, and R. I. Werley, Jr., Department of
Chemistry, University of California, Riverside, CA 92521
- 2467 Palladium(0)-Catalyzed Reaction of 1-Alkenylboronates with Vinyllic
Halides: Synthesis of (1Z,3E)-1-Phenyl-1,3-octadiene
N. Miyaoura and A. Suzuki, Department of Applied Chemistry, Faculty of
Engineering, Hokkaido University, Sapporo 060, Japan
- 2470 Trimethylsilyldiazomethane
T. Shioiri, T. Aoyama, and S. Mori, Faculty of Pharmaceutical
Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467,
Japan
- 2471 Domino Diels-Alder Reaction
R. T. Taylor, M. W. Pelter, and L. A. Paquette, Department of
Chemistry, Miami University, Oxford, OH 45056

CUMULATIVE AUTHOR INDEX

FOR VOLUMES 65 AND 66

This index comprises the names of contributors to Volume 65 and 66 only. For authors to previous volumes, see cumulative indices in Volume 64, which covers Volumes 60 through 64, and Volume 59, which covers Volumes 55 through 59, and either indices in Collective Volumes I through V or single volumes entitled *Organic Syntheses, Collective Volumes, I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

- | | |
|-----------------------------------|----------------------------------|
| Abrams, S. R., 66, 127 | Fowler, K. W., 65, 108 |
| Almond, M. R., 66, 132 | Fox, C. M. J., 66, 108 |
| Aslamb, M., 65, 90 | Frye, S. V., 65, 215 |
| | Fujisawa, T., 66, 116, 121 |
| Raba, S., 66, 60 | |
| Bankston, D., 66, 180 | Georg, G. I., 65, 32 |
| Bercaw, J. E., 65, 42 | Giese, B., 65, 236 |
| Bergman, J., 65, 146 | Goodwin, G. R. T., 65, 1 |
| Bergman, R. G., 65, 42 | Gross, A. W., 65, 166 |
| Block, E., 65, 90 | |
| Boger, D. L., 65, 32, 98; 66, 142 | Haese, W., 65, 26 |
| Boeckman, R. K., Jr., 66, 194 | Hanessian, S., 65, 243 |
| Bou, A., 65, 68 | Hegedus, L. S., 65, 140 |
| Braxmeier, H., 65, 159 | Holmes, A. B., 65, 52, 61 |
| Brotherton, C. E., 65, 32 | Hobbs, F. W., Jr., 66, 52 |
| Brown, C. A., 65, 224 | Hormi, O., 66, 173 |
| Büchi, G. H., 66, 29 | Hsiao, C.-N., 65, 135 |
| Buter, J., 65, 150 | Huang, Z., 66, 211 |
| | |
| Chang, T. C. T., 66, 95 | Imwinkelried, R., 65, 230 |
| Corey, E. J., 65, 166 | |
| | Jadhav, P. K., 65, 224 |
| Danheiser, R. L., 66, 1, 8, 14 | Jones, G. E., 65, 52 |
| Davidson, S. K., 65, 119 | |
| Davis, F. A., 66, 203 | Kellogg, R. M., 65, 150 |
| Dupuis, J., 65, 236 | Kendrick, D. A., 65, 52 |
| | King, A. O., 66, 67 |
| Eliel, E. L., 65, 215 | Kipphardt, H., 65, 173, 183 |
| Enders, D., 65, 173, 183 | Koppenhoefer, B., 66, 151, 160 |
| Engler, A., 66, 37 | Kresze, G., 65, 159 |
| | Kuhlmann, H., 65, 26 |
| Fey, P., 65, 173, 183 | Kume, F., 65, 215 |
| Fink, D. M., 66, 1, 8, 14 | Kuwajima, I., 65, 17; 66, 43, 87 |

Le Gal, J. Y., 65, 47
Ley, S. V., 66, 108
Lombardo, L., 65, 81
Loudon, G. M., 66, 132
Lynch, J. E., 65, 215

Macdonald, J. E., 66, 194
Martin, S. F., 65, 119
Maruoka, K., 66, 185
Masuda, T., 66, 22
McGuire, M. A., 65, 140
Mickel, S. J., 65, 135
Miller, M. J., 65, 135
Mimura, S., 66, 22
Mook, R., Jr., 66, 75
Mukaiyama, T., 65, 6
Mullican, M. D., 65, 98
Munsterer, H., 65, 159

Nakai, S., 66, 185
Nakamura, E., 65, 17; 66, 43
Narasaka, K., 65, 6, 12
Negishi, E.-i., 66, 60, 67
Nix, M., 65, 236
Nugent, W. A., 66, 52

Okano, K., 66, 14
Olomucki, M., 65, 47
Ort, O., 65, 203

Panek, J. S., 66, 142
Pericas, M. A., 65, 68
Perni, R. B., 66, 194
Phillips, G. W., 65, 119
Poulter, C. D., 66, 211

Ramnaud, M., 66, 220
Riera, A., 65, 68
Rodgers, W. B., 65, 108
Rosenblum, M., 66, 95

Sand, P., 65, 146
Sato, T., 66, 116, 121
Schiess, M., 65, 230
Schultze, L. M., 65, 140
Schurig, V., 66, 151, 160
Seebach, D., 65, 230
Seidler, P. F., 65, 42
Serratos, F., 65, 68
Shaw, A. C., 66, 127
Sher, P. M., 66, 75
Simms, N., 66, 95
Smith, G. C., 65, 1
Spitzner, D., 66, 37

Sporikou, C. N., 65, 61
Stetter, H., 65, 26
Stimmel, J. B., 66, 132
Stringer, O. D., 66, 203
Stryker, J. M., 65, 42
Szczepanski, S. W., 66, 14

Takahashi, T., 66, 60, 67
Takeda, A., 66, 22
Thomas, A. J., 66, 194
Thompson, E. A., 66, 132
Threlkel, R. S., 65, 42
Tsai, Y.-M., 66, 1, 8, 14
Tsuboi, S., 66, 22

Urabe, H., 66, 87

Villieras, J., 66, 220
Vishwakarma, L. C., 66, 203
Vogel, D. E., 66, 29

Walshe, N. D. A., 65, 1
Wester, R. T., 65, 108
Woodward, F. E., 65, 1
Woodside, A. B., 66, 211

Yamamoto, H., 66, 185
Yasuda, M., 66, 142

Ziegler, F. E., 65, 108

CUMULATIVE SUBJECT INDEX

FOR VOLUMES 65 AND 66

This index comprises subject matter for Volumes 65 and 66 only. For subjects in previous volumes, see the cumulative indices in Volume 64, which covers Volumes 60 through 64, and Volume 59, which covers Volumes 55 through 59, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in brackets. While the systematic name is indexed separately, it also accompanies the common name. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester, [1R-(1 α ,2 β ,5 α)]-, **65**, 203

Acetic acid, (diethoxyphosphinyl)-, ethyl ester; (867-13-0), **66**, 224

Acetic acid ethenyl ester, **65**, 135

Acetic acid, hydrazinoimino-, ethyl ester; (53085-26-0), **66**, 149

Acetic acid, trifluoro-, anhydride, **65**, 12

Acetic acid vinyl ester, **65**, 135

ACETONE TRIMETHYLSILYL ENOL ETHER: SILANE, (ISOPROPENYLOXY)TRIMETHYL-; SILANE, TRIMETHYL[(1-METHYLETHENYL)OXY]-; (1833-53-0), **65**, 1

Acetonitrile, purification, **66**, 101

Acetophenone; Ethanone, 1-phenyl-; (98-86-2), **65**, 6, 119

Acetophenone silyl enol ether: Silane, trimethyl[(1-phenylvinyl)oxy]-; Silane, trimethyl[(1-phenylethenyl)oxy]-; (13735-81-4), **65**, 12

4-ACETOXYAZETIDIN-2-ONE: 2-AZETIDINONE, 4-HYDROXY-ACETATE (ESTER): 2-AZETIDINONE, 4-(ACETOXY)-; (20562-53-0), **65**, 135

Acetylene; Ethyne; (74-86-2), **65**, 61

α , β -Acetylenic esters from β -chloroalkylidene malonates, **66**, 178

3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(5H)-ONE, **66**, 108, 110

Acrylonitrile; 2-Propenenitrile; (107-13-1), **65**, 236

Acy chlorides, preparation, **66**, 116

Arylsilanes, preparation, **66**, 18

ADDITION OF TIN RADICALS TO TRIPLE BONDS, **66**, 75

Adipic acid monomethyl ester; (627-91-8), **66**, 116, 117, 120

Alane, (E)-1-decenyldiisobutyl-, **66**, 60, 61

(S)-Alanine (L-alanine); (56-41-7), **66**, 151-153, 159

Aldehydes, preparation from carboxylic acid, **66**, 124

Aldol reaction, **65**, 6, 12

Alkenylzinc reagents, **66**, 64
 Alkylation, of ester enolate, **66**, 87
 (R)-Alkyloxiranes, properties, **66**, 169
 (R)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY, **66**, 160
 ALKYNE ISOMERIZATION, **66**, 127
 Allene, 1-Methyl-1-(trimethylsilyl)-, **66**, 8, 9
 Allenes, synthesis by Claisen rearrangement, **66**, 22
 β -Allenic esters, conjugation by alumina, **66**, 26
 ALLENYLSILANES, SYNTHESIS OF, **66**, 1
 Allyl alcohol; (107-18-6), **66**, 14, 16, 21
 ALLYL CARBAMATES, **65**, 159
 (E)-3-Allyloxyacrylic acids, **66**, 33, 34
 Allyl trimethylsilyl ether, metallation, **66**, 18
 Aluminum chloride, **66**, 90
 Aluminum oxide, **66**, 23
 Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7), **66**, 193
 Aluminum, tripropyl-, (102-67-0), **66**, 193
 Amberlyst 15 ion exchange resin, **66**, 203, 206
 Amino acids, determination of enantiomeric purity, **66**, 153
 1-AMINO-2-METHOXYMETHYLPYRROLIDINE, (R) (+) (RAMP), **65**, 173
 1-AMINO-2-METHOXYMETHYLPYRROLIDINE, (S)-(-) (SAMP), **65**, 173, 183
 3-Aminopropylamine: 1,3-Propanediamine; (109-76-2), **65**, 224
 Ammonia, **66**, 133, 135
 [3+3] Annulation, **66**, 4, 8, 10, 11
 Asymmetric synthesis, **65**, 183, 215
 AZA-ENE REACTION. **65**, 159
 1H-Azepine, hexahydro-2-propyl-, (85028-29-1), **66**, 193

2-AZETIDINONE, 4-(ACETOXY)-, 65, 135

2-AZETIDINONE, 4-HYDROXY-ACETATE (ESTER), 65, 135

2-AZETIDINONE, 3-METHOXY-1,3-DIMETHYL-4-PHENYL-, 65, 140

Azobisisobutyronitrile (AIBN); (78-67-1), 66, 77, 79, 86

Deckmann rearrangement, 66, 185, 189, 190

Benzaldehyde; (100-52-7), 65, 119; 66, 203

Benzaldehyde, 2-bromo-4,5-dimethoxy-, 65, 108

Benzeneamine, 2-methyl-3-nitro-, 65, 146

1,2-Benzenediol; (120-80-9), 66, 184

Benzenemethanethiol, 65, 215

Benzenesulfonamide, 66, 203

2H-1-BENZOPYRAN-3-CARBOXYLIC ACID, 5,6,7,8-TETRAHYDRO-2-OXO-,
METHYL ESTER, 65, 98

4H-1,3-BENZOXATHIIN, HEXAHYDRO-4,4,7-TRIMETHYL-, 65, 215

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride; (4568-71-2),
65, 26

N-Benzylidenebenzenesulfonamide; (13909-34-7), 66, 203, 204, 206, 210

Benzylidenemalononitrile: Malononitrile, benzylidene-; Propanedinitrile,
(phenylmethylene)-; (2700-22-3), 65, 32

Benzyl mercaptan: α -Toluenethiol; Benzenemethanethiol; (100-53-8), 65, 215

Benzyltriethylammonium chloride, 66, 204

BETA-LACTAM, 65, 135, 140

BIARYL SYNTHESIS, 66, 67

Biaryls, preparation by Pd-catalyzed aryl-aryl coupling, 66, 73

BICYCLO[3.1.1]HEPTANE, 6,6-DIMETHYL-2-METHYLENE-, (1S)-, 65, 224

BICYCLO[3.1.1]HEPT-2-ENE, 2,6,6-TRIMETHYL-, (1S)-, 65, 224

Bicyclo[2.2.2]octan-2-ones, preparation, 66, 37, 40
 [1,1'-BIPHENYL]-2,2'-DICARBOXALDEHYDE, 4,4',5,5'-TETRAMETHOXY-, 65, 108
 Biphenyl, 2-methyl-4'-nitro-; (33350-73-1), 66, 74
 1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE: 2,7-DISILOCTA-3,5-DIYNE,
 2,2,7,7-TETRAMETHYL-; SILANE, 1,3-BUTADIYNE-1,4-DIYLBIS[TRIMETHYL-;
 (4526-07-2), 65, 52
 1,2-Bis(trimethylsilyloxy)cyclobut-1-ene: Silane, (1-cyclobuten-1,2-
 ylenedioxy)bis[trimethyl-; Silane, [1-cyclobutene-1,2-
 diylbis(oxy)]bis[trimethyl-; (17082-61-0), 65, 17
 Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃)
 (1:1); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1);
 (109-63-7), 65, 17
 2-Bromo-2-butene (cis and trans mixture): 2-Butene, 2-bromo-;
 (13294-71-8), 65, 42
 1-Bromo-3-chloro-2,2-dimethoxypropane: 2-Propanone, 1-bromo-3-chloro,
 dimethyl acetal; Propane, 1-bromo-3-chloro-2,2-dimethoxy-;
 (22089-54-9), 65, 2
 6-Bromo-3,4-dimethoxybenzaldehyde: Benzaldehyde, 2-bromo-4,5-dimethoxy-;
 (5392-10-9), 65, 108
 6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine,
 N-[(2-bromo-4,5-dimethoxyphenyl)methylene]-; (73252-55-8), 65, 108
 BROMOMETHANESULFONYL BROMIDE: METHANESULFONYL BROMIDE, BROMO-;
 (54730-18-6), 65, 90
 2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane: 1,3-Dioxane, 2-(bromomethyl)-
 2-(chloromethyl)-; (60935-30-0), 65, 32
 N-Bromomethylphthalimide: Phthalimide, N-(bromomethyl)-; 1H-Isoindole-
 1,3-(2H)-dione, 2-(bromomethyl)-; (5332-26-3), 65, 119

1-Bromo-4-nitrobenzene, **66**, 68

N-BROMOSUCCINIMIDE: SUCCINIMIDE, N-BROMO-; 2,5,-PYRROLIDINEDIONE, 1-BROMO-;
(128-08-5), **65**, 243

o-Bromotoluene, **66**, 69

Brook rearrangement, **66**, 19

Dutadiyne, **65**, 52

Butane, 1-chloro-, **65**, 61

Butanedioic acid, dioxo-, diethyl ester; (59743-08-7), **66**, 149

Butanedioic acid, tetrahydroxy-, disodium salt; (866-17-1), **66**, 149

1-Butanone, 3-hydroxy-3-methyl-1-phenyl-, **65**, 6, 12

2-Butene, 2-bromo-, **65**, 42

2-Butene, 1-bromo-3-methyl-, (870-63-3), **66**, 85

2-Butene, 2-methyl-, **65**, 159

2-Butenoic acid, 2-methyl-, methyl ester, (E); (6622-76-0), **66**, 94

2-Buten-1-one, 3-methyl-1-phenyl-, **65**, 12

3-Buten-2-one; (78-94-4), **65**, 26

tert-BUTYL ACETOTHIOACETATE; (15925-47-0), **66**, 108, 112, 114

Butyl bromide, **66**, 118

tert-Butylhydrazine hydrochloride: Hydrazine, tert-butyl, monohydrochloride;
Hydrazine, (1,1-dimethylethyl)-, monohydrochloride; (7400-27-3), **65**, 166

3-tert-Butyl-4-hydroxy-5-methylphenyl sulfide, **66**, 16

tert-Butyllithium, **66**, 15, 16, 18, 67, 69

Butyllithium: Lithium, butyl-, (109-72-8), **65**, 98, 108, 119;

66, 14, 16, 37, 39, 88, 194, 196

Butylmagnesium bromide, **66**, 116, 118

N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine: 2-Pentanamine,
 N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-2,4,4-trimethyl-;
 (90545-93-0), **65**, 166

TERT-BUTYL-TERT-OCTYLAMINE: 2-PENTANAMINE, N-(1,1-DIMETHYLETHYL)-2,4,4-
 TRIMETHYL-; (90545-94-1), **65**, 166

S-tert-Butyl 3-oxobutanethioate, **66**, 108, 109

2-BUTYNOIC ACID, 4-CHLORO-, METHYL ESTER, **65**, 47

Carbamic acid, dichloro-, methyl ester, **65**, 159

CARBAMIC ACID, (2-METHYL-2-BUTENYL)-, METHYL ESTER, **65**, 159

Carbamic acid, methyl ester, **65**, 159

Carboalumination of alkynes, **66**, 64

Carbocupration of alkynes, **66**, 65

1-Carbomethoxy-1-methylethyl-3-oxobutanoate, **66**, 110

2-CARBOMETHOXY-3-VINYLCYCLOPENTANONE; (75351-19-8), **66**, 52, 53, 56, 59

Carbonic acid, dicesium salt, **65**, 150

Carbonochloridic acid, methyl ester, **65**, 47

Carboxylic acids, reduction, **66**, 160

(E)-(Carboxyvinyl)trimethylammonium betaine; (54299-83-1), **66**, 29, 30, 33, 36

(R)-(-)-Carvone; (6485-40-1), **66**, 8, 9, 13

Catechol, **66**, 180, 182

Cellulose chromatography, **66**, 213, 216

Cesium carbonate: Carbonic acid, dicesium salt; (534-17-8), **65**, 150

CESIUM THIOLATES, **65**, 150

Chiral auxiliary, **65**, 173, 183, 203, 215

Chirasil-Val, **66**, 153, 154

Chloroacetaldehyde diethyl acetal; (621-62-5), **66**, 96, 100, 107

(S)-2-Chloroalkanoic acids

determination of enantiomeric purity, **66**, 154

properties, **66**, 155

(S)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY, **66**, 151

(S)-2-CHLOROALKANOIC ACIDS VIA (S)-2-CHLORO-1-ALKANOLS, **66**, 160

(S)-2-Chloroalkan-1-ols, properties, **66**, 168

1-Chlorobutane: Butane, 1-chloro-; (109-69-3), **65**, 61

α -Chloroamines, **66**, 119

2-Chloroethanol; Ethanol, 2-chloro-; (107-07-3), **65**, 150

2-Chloroethyl dichlorophosphate: Phosphorodichloridic acid, 2-chloroethyl ester; (1455-05-6), **65**, 68

Chlorohydrins, preparation from α -chloro acids, **66**, 161

(S)-2-Chloro-3-methylbutan-1-ol, **66**, 164

6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one; (81956-31-2), **66**, 194, 195, 202

2S,3S)-2-Chloro-3-methylpentanoic acid, **66**, 154

(2S,3S)-2-Chloro-3-methylpentan-1-ol, **66**, 164

(S)-2-Chloro-4-methylpentan-1-ol, **66**, 164

m-Chloroperoxybenzoic acid, **66**, 204

(S)-2-CHLOROPROPANOIC ACID; (29617-66-1), **66**, 151, 154, 159, 160, 172

(S)-2-Chloropropan-1-ol; (19210-21-0), **66**, 160, 164, 172

N-Chlorosuccinimide; (128-09-6), **66**, 211, 214, 219

Chlorosulfonyl isocyanate: Sulfuryl chloride isocyanate; (1189-71-5), **65**, 135

Chlorotetrolic esters, **65**, 47

1-Chloro-N,N,2-trimethylpropenylamine; (26189-59-3). **66**, 116, 117, 119, 120

Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4), **65**, 1, 6, 61;
66, 14, 16, 21, 44

as catalyst for conjugate addition, **66**, 47

1-Chloro-3-trimethylsilylpropane; (2344-83-4), **66**, 88, 90, 94

Chromium carbonyl, **65**, 140

Chromium hexacarbonyl: Chromium carbonyl (OC-6-11); (13007-92-6), **65**, 140

Chromium, pentacarbonyl(1-methoxyethylidene)-, **65**, 140

Cinnamyl alcohol; (104-54-1), **66**, 30, 32, 36

Claissen rearrangement, of propargyl alcohols, **66**, 22

CONJUGATE ADDITION/CYCLIZATION OF A CYANOCUPRATE, **66**, 52

CONJUGATE ADDITION, ZINC HOMOENOLATES TO ENONES, **66**, 43, 50

CONJUGATED DIENES, SYNTHESIS OF, **66**, 60, 64

Copper(I) bromide (7787-70-4), **65**, 203; **66**, 2, 3, 44, 45

Copper, bromo[thiobis[methane]]-; (54678-23-8), **66**, 51

Copper chloride (CuCl); (7758-89-6), **66**, 180, 182, 184

Copper(I) chloride - tetramethylethylenediamine complex, **65**, 52

Copper cyanide (CuCN), **66**, 53, 55

Copper iodide (CuI), **66**, 97, 100, 116, 118

Cuprate addition, **66**, 52, 95

Cuprate, dibutyl-, lithium, reaction with acetylene, **66**, 62

Cuprates, higher order, **66**, 57

Cuprous bromide/dimethyl sulfide; (54678-23-8), **66**, 51

Cuprous chloride-pyridine complex, **66**, 182

[2 + 2] CYCLOADDITION, **65**, 135

Cyclobutanecarboxamide; (1503-98-6), **66**, 132, 134, 136, 141

Cyclobutanecarboxylic acid; (3721-95-7), **66**, 133, 135, 141

CYCLOBUTYLAMINE, **66**, 132

Cyclobutylamine hydrochloride; (6291-01-6), **66**, 134, 135, 141

Cyclohexanamine, **65**, 108

Cyclohexanamine, N-[(2-bromo-4,5-dimethoxyphenyl)methylene]-, **65**, 108

Cyclohexanamine, N-[(2-iodo-4,5-dimethoxyphenyl)methylene]-, **65**, 108
 Cyclohexane, 1,1-diethoxy-, **65**, 17
 CYCLOHEXANE, 1,2-BIS(METHYLENE)-, **65**, 90
 CYCLOHEXANE, 1,2-DIMETHYLENE, **65**, 90
 CYCLOHEXANE, 5-METHYL-1-METHYLENE-2-(1'-METHYLETHYL)-, R,R-, **65**, 81
 CYCLOHEXANEBUTANOIC ACID, γ -OXO-, ETHYL ESTER, **65**, 17
 Cyclohexanol, 2-(1-mercapto-1-methylethyl)-5-methyl-, [(1R-(1 α ,2 α ,5 α))-],
65, 215
 Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2 β ,5 β)], **65**, 81
 CYCLOHEXANOL, 5-METHYL-2-(1-METHYL-1-PHENYLETHYL)-, [1R-(1 α ,2 β ,5 α))-], **65**, 203
 Cyclohexanone; (108-94-1), **65**, 98
 Cyclohexanone diethyl ketal; Cyclohexane, 1,1-diethoxy-; (1670-47-9), **65**, 17
 Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)-, **65**, 81
 CYCLOHEXANONE, 5-METHYL-2-(1-METHYLETHYLIDENE)-, (R)-, **65**, 203, 215
 Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)-, **65**, 203
 Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)-, **65**, 203
 Cyclohexanone, 5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]-,
 (2R-trans)-; (79563-58-9); (2S-cis)-; (79618-04-5), **65**, 215
 Cyclohexanone oxime; (100-64-1), **66**, 185, 187, 193
 Cyclohexanone oxime methanesulfonate; (80053-69-6), **66**, 185, 186, 193
 Cyclohexene, 1-methyl-, **65**, 90
 2-Cyclohexen-1-one; (930-68-7), **66**, 44, 45, 51, 95, 97, 101, 107
 2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-,
 ethyl ester; (90147-64-1), **66**, 51
 Cyclohexylamine; Cyclohexanamine; (108-91-8), **65**, 108
 1,3-CYCLOPENTADIENE, 1,2,3,4,5-PENTAMETHYL-, **65**, 42
 Cyclopentadienes. synthesis. **66**. 11

Cyclopentanes, synthesis, **66**, 10
 CYCLOPENTANONE SYNTHESIS, **66**, 87, 92, 93
 Cyclopentanone, 2-carbomethoxy-3-vinyl, **66**, 56
 Cyclopentanone, 2-ethenyl-2-methyl; (88729-76-4), **66**, 94
 2-CYCLOPENTEN-1-ONE, 3-METHYL-2-PENTYL-, **65**, 26
 Cyclopropane, 1-trimethylsilyloxy-1-ethoxy-, **66**, 44
 Cyclopropanecarboxylic acid chloride, **66**, 176
 CYCLOPROPENONE 1,3-PROPANEDIOL KETAL: 4,8-DIOXASPIRO[2.5]OCT-1-ENE;
 (60935-21-9), **65**, 32
 Cyclopropylpropionic acid ethyl ester, **66**, 177

 Davis reagent, **66**, 203
 Decanoic acid, 6-oxo-; (4144-60-9), **66**, 126
 Decanoic acid, 6-oxo-, methyl ester; (61820-00-6), **66**, 120
 (E)-1-Decenyldiisobutylalane, **66**, 60, 61
 1-Decyne; (764-93-2), **66**, 60, 61, 66
 2-DECYN-1-OL; (4117-14-0), **66**, 127, 128, 131
 9-DECYN-1-OL; (17643-36-6), **66**, 127, 128, 131
 1-DEOXY-2,3,4,6-TETRA-O-ACETYL-1-(2-CYANOETHYL)- α -D-GLUCOPYRANOSE:
 D-GLYCERO-D-IDO-NONONONITRILE, 4,8-ANHYDRO-2,3-DIDEOXY-,
 5,6,7,9-TETRAACETATE; (86563-27-1), **65**, 236
 (I,I-Diacetoxyiodo)benzene, **66**, 136
 DIALKOXYACETYLENES, **65**, 68
 1,3-Diaminopropane; (109-76-2), **66**, 127, 128, 131
 Diazotization of amino acids, **66**, 151, 156
 Dibromomethane: Methane, dibromo-; (74-95-3), **65**, 81

1,2-Di-tert-butoxy-1-chloroethene, (E)-: Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E); (70525-93-8), **65**, 58

1,2-Di-tert-butoxy-1,2-dichloroethane, dl-: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy1)]bis(oxy)bis[2-methyl-, (R*,R*)-(±)-; (68470-80-4), **65**, 68

1,2-Di-tert-butoxy-1,2-dichloroethane, meso-: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy1)bis(oxy)]bis[2-methyl-, (R*,S*)-; (68470-81-5), **65**, 68

2,3-Di-tert-butoxy-1,4-dioxane, cis-: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis-; (68470-78-0), **65**, 68

2,3-Di-tert-butoxy-1,4-dioxane, trans-: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans-; (68470-79-1), **65**, 68

DI-TERT-BUTOXYETHYNE: PROPANE, 2,2'-[1,2-ETHYNEDIYLBIS(OXY)]BIS[2-METHYL-; (66478-63-5), **65**, 68

Dicarbonyl(cyclopentadienyl)diiron, [(CO)₂CpFe]₂; (12154-95-9), **66**, 96, 99, 106

Dicarbonyl(cyclopentadienyl)(ethyl vinyl ether)iron tetrafluoroborate, **66**, 96, 106

Dicarbonyl(cyclopentadienyl)(trans-3-methyl-2-vinylcyclohexanone)iron tetrafluoroborate, **66**, 97

2,3-Dichloro-1,4-dioxane, trans-: 1,4-Dioxane, 2,3-dichloro-, trans-; (3883-43-0), **65**, 68

(1,1-Dichloroiodo)benzene, **66**, 137

5,5-Dicyano-4-phenylcyclopent-2-enone 1,3-propanediol ketal: 6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-; (88442-12-0), **65**, 32

Dicyclopentadiene, **66**, 99

Dieckmann cyclization, **66**, 52

DIELS-ALDER REACTION. INVERSE ELECTRON DEMAND. **66**, 142, 147, 148

Diels-Alder reaction of triethyl 1,2,4-triazine-3,5,6-tricarboxylate, **66**, 150

Diels-Alder reactions, **66**, 40

Diethylamine, **66**, 145

Diethyl aminomethylphosphonate: Phosphonic acid, (aminomethyl)-, diethyl ester; (50917-72-1), **65**, 119

DIETHYL N-BENZYLIDENEAMINOMETHYLPHOSPHONATE: PHOSPHONIC ACID, [[(PHENYLMETHYLENE)AMINO]METHYL]-, DIETHYL ESTER; (50917-73-2), **65**, 119

Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate, **66**, 173, 174

Diethyl cyclopropylcarbonylmalonate; (7394-16-3), **66**, 175, 179

Diethyl cyclopropylmalonate, **66**, 173

Diethyl dioxosuccinate; (59743-08-7), **66**, 144, 149

Diethyl isocyanomethylphosphonate: Phosphonic acid, (isocyanomethyl)-, diethyl ester; (41003-94-5), **65**, 119

Diethyl malonate; (105-53-3), **66**, 175, 179

Diethyl oxalate: Oxalic acid, diethyl ester; Ethanedioic acid, diethyl ester; (95-92-1), **65**, 146

Diethyl phosphite; (762-04-9), **66**, 195, 197, 202

6-DIETHYLPHOSPHONOMETHYL-2,2-DIMETHYL-1,3-DIOXEN-4-ONE, **66**, 194-196, 202

Diethyl phthalimidomethylphosphonate: Phosphonic acid, (phthalimidomethyl)-, diethyl ester; Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-methyl]-, diethyl ester; (33512-26-4), **65**, 119

DIHYDROJASMONE, **65**, 26

1,2-Dihydroxybenzene; (120-80-9), **66**, 180, 184

Dihydroxytartaric acid disodium salt hydrate; (866-17-1), **66**, 144, 146, 149

Diisobutylaluminum hydride; (1191-15-7), **66**, 60, 62, 66, 186, 188, 193

Diisopropylamine; 2-Propanamine, N-(1-methylethyl)-; (108-18-9), **65**, 98;

66, 37, 39, 88, 194

DIISOPROPYL (2S,3S)-2,3-O-ISOPROPYDIDENNETARTRATE: 1,3-DIOXOLANE-4,5-

DICARBOXYLIC ACID, 2,2-DIMETHYL-, BIS(1-METHYLETHYL) ESTER, (4R-TRANS)-;

(81327-47-1), **65**, 230

Diketene; (674-82-8), **66**, 109, 111, 114

1,1-Dimethoxyethylene: Ethene, 1,1-dimethoxy-; (922-69-0), **65**, 98

3,3-Dimethylallyl bromide; (870-63-3), **66**, 76, 78, 85

4-(N,N-Dimethylamino)pyridine: Pyridine, 4-(dimethylamino)-;

4-Pyridinamine, N,N-dimethyl-; (1122-58-3), **65**, 12

N,N-Dimethylchloromethylenammonium chloride; (3724-43-4),

66, 121, 122, 124, 126

Dimethyl diazomethylphosphonate: Phosphonic acid, (diazomethyl)-, dimethyl ester; (27491-70-9), **65**, 119

3,3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE: 1,5-PENTANEDIONE,

3,3-DIMETHYL-1,5-DIPHENYL-; (42052-44-8), **65**, 12

1,2-DIMETHYLENECYCLOHEXANE: CYCLOHEXANE, 1,2-DIMETHYLENE; CYCLOHEXANE,

1,2-BIS(METHYLENE)-; (2019-40-9), **65**, 90

N,N-Dimethylformamide, **66**, 121, 123, 195, 197

Dimethyl (E)-2-hexenedioate; (70353-99-0), **66**, 52, 53, 59

N,N-Dimethylisobutyramide, **66**, 117, 118

Dimethyl (2S,3S)-2,3-O-isopropylidenetartrate: 1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester, (4R-trans)- or (4S-trans)-;

(37031-29-1) or (37031-30-4), **65**, 230

Dimethyl malonate; (108-59-8), **66**, 76, 78, 85

Dimethyl methoxymethylenemalonate: Malonic acid, (methoxymethylene)-, dimethyl ester; Propanedioic acid, (methoxymethylene)-, dimethyl ester; (22399 14-7), **65**, 98

1,3-DIMETHYL-3-METHOXY-4-PHENYL AZETIDINONE: 2-AZETIDINONE, 3-METHOXY-1,3-DIMETHYL-4-PHENYL-; (82918-98-7), **65**, 140

1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid, **66**, 38

N,N'-Dimethylpropyleneurea (DMPU); (7226-23-5), **66**, 45, 91, 94

Dimethyl sulfide, **66**, 211

Dimethyl sulfoxide. **66**. 15. 17

1,9-DIMETHYL-8-(TRIMETHYLSILYL)BICYCLO[4.3.0]NON-8-EN-2-ONE, **66**, 8

1,3-Dioxane, 2-(bromomethyl)-2-(chloromethyl)-, **65**, 32

1,4-Dioxane, 2,3-dichloro-, trans-, **65**, 68

1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans-, **65**, 68

1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis-, **65**, 68

6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-, **65**, 32

4,8-DIOXASPIRO[2.5]OCT-1-ENE, **65**, 32

p-Dioxino[2,3,-b]-p-dioxin, hexahydro, **65**, 68

[1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro, **65**, 68

1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester, (4R-trans)- or (4S-trans)-, **65**, 230

1,3-DIOXOLANE-4,5-DICARBOXYLIC ACID, 2,2-DIMETHYL-, BIS(1-METHYLETHYL) ESTER, (4R-TRANS)-, **65**, 230

2,7-DISILA OCTA-3,5-DIYNE, 2,2,7,7-TETRAMETHYL-, **65**, 52

Disodium dihydrogen pyrophosphate; (7758-16-9), **66**, 214, 219

3,7-Dithianonane-1,9-diol: Ethanol, 2,2'-(trimethylenedithiol)di-; Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis-; (16260-48-3), **65**, 150

3,7-Dithianonane-1,9-dithiol: Ethanethiol, 2,2'-(trimethylenedithio)di-;
 Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis-; (25676-62-4), **65**, 150

DMAP, **65**, 12

Dowex AG 50W-X8 cation exchange resin, **66**, 212, 214, 215

Enamines, α -chloro, **66**, 119

Enamines, as Diels-Alder dienophiles, **66**, 147

Enolate chlorination, **66**, 194

Epoxide formation, from chlorohydrin, **66**, 160

Ester enolate alkylation, **66**, 87

Ester hydrolysis, **66**, 38, 87, 89

Ethane, hexachloro- (67-72-1), **66**, 202

Ethane, 1,1',1''-[methylidynetris(oxy)]tris-, **65**, 146

Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1), **65**, 17

Ethanedioic acid, diethyl ester, **65**, 146

Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis-, **65**, 150

Ethanethiol, 2,2'-(trimethylenedithio)di-, **65**, 150

Ethanol, **66**, 175

Ethanol, 2-chloro-, **65**, 150

Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis-, **65**, 150

Ethanol, 2,2'-(trimethylenedithiol)di-, **65**, 150

Ethanone, 1-phenyl-, **65**, 6, 119

Ethene, 1,1-dimethoxy-, **65**, 98

1-(1-Ethoxyethoxy)-1,2-propadiene, metallation, **66**, 18

Ethyl α -(bromomethyl)acrylate; (17435-72-2), **66**, 222, 224

Ethyl chloroformate; (541-41-3), **66**, 133, 135, 141

Ethyl cyanoformate; (623-49-4), **66**, 143, 149

ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE: CYCLOHEXANEBUTANOIC ACID, γ -OXO-, ETHYL ESTER; (54966-52-8), **65**, 17

ETHYL CYCLOPROPYLPROPIOLATE, **66**, 173, 174

ETHYL (E,Z)-2,4-DECADIENOATE; (3025-30-7), **66**, 22, 23, 25, 28

Ethyl 3,4-decadienoate; (36186-28-4), **66**, 22, 28

Ethylenediaminetetraacetic acid, tetrasodium salt: Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)]-, tetrasodium salt, trihydrate; (67401-50-7), **65**, 166

Ethyl ether, compd. with boron fluoride (BF₃) (1:1), **65**, 17

ETHYL α -(HYDROXYMETHYL)ACRYLATE; (10029-04-6), **66**, 220, 222, 224

Ethyl N-(2-methyl-3-nitrophenyl)formimidate, **65**, 146

Ethyl oxalamidrazonate; (53085-26-0), **66**, 143, 146, 149

Ethyl propiolate; (623-47-2), **66**, 29, 31, 36

Ethyl thioamidooxalate; (16982-21-1), **66**, 143, 145, 149

Ethyne, **65**, 61

Finkelstein reaction, **66**, 87

Flash chromatography, **66**, 135, 196

Florisil, **66** 197

Formaldehyde, **66**, 220

Formic acid, chloro-, ethyl ester; (541-41-3), **66**, 141

Formic acid, chloro-, methyl ester, **65**, 47

Formic acid, cyano-, ethyl ester; (623-49-4), **66**, 149

Geraniol; (106-24-1), **66**, 211, 214, 219

Geranyl chloride; (5389-87-7), **66**, 211, 212, 214, 219

GERANYL DIPHOSPHATE, TRISAMMONIUM SALT, **66**, 211-213

Glucopyranoside, methyl, α -D-, **65**, 243

Glucopyranoside, methyl 4,6-O-benzylidene-, α -D-, **65**, 243
 GLUCOPYRANOSIDE, METHYL 6-BROMO-6-DEOXY, 4-BENZOATE, α -D-, **65**, 243
 Glucopyranoside, methyl 4,6-O-(phenylmethylene)-, α -D-, **65**, 243
 Glucopyranosyl bromide, 2,3,4,6-tetraacetate, α -D-, **65**, 236
 Glucopyranosyl bromide tetraacetate, α -D-, **65**, 236
 GLYCERO D IDO-NONONONITRILE, 4,8-ANHYDRO-2,3-DIDEOXY-, 5,6,7,9-TETRAACETATE, α -D-, **65**, 236
 Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)]-, tetrasodium salt, trihydrate, **65**, 166
 Grignard reagents, reaction with acyl chlorides, **66**, 116
 Grob Fragmentation, **66**, 173
 Halide exchange reaction, **66**, 87
 2,5-Heptadien-4-ol, 3,4,5-trimethyl-, **65**, 42
 Heptanal; (111-71-7). **65**, 26
 3-HEPTANONE, 4-METHYL-, (S)-, **65**, 183
 Hexachloroethane; (67-72-1), **66**, 195, 197, 202
 (5Z,7E)-5,7-HEXADECADIENE, **66**, 60, 61, 63
 HEXAHYDRO-4,4,7-TRIMETHYL-4H-1,3-BENZOXATHIIN: 4H-1,3-BENZOXATHIIN, HEXAHYDRO-4,4,7-TRIMETHYL-; (59324-06-0), **65**, 215
 Hexamethylphosphoric triamide (HMPA); (680-31-9), **66**, 44, 45, 51, 88, 94
 Hexanedioic acid, monomethyl ester; (627-91-8), **66**, 120
 2,4-Hexenedioic acid, monomethyl ester, (Z,Z)-; (61186-96-7), **66**, 184
 1-Hexene, 1-iodo-, (E); (16644-98-7), **66**, 66
 1-Hexene, 1-iodo-, (Z); (16538-47-9), **66**, 66
 (E)-1-Hexenyl diisobutylalane; (20259-40-9), **66**, 66
 (E)-1-Hexenyl iodide; (16644-98-7), **66**, 63, 66

(Z)-1-Hexenyl iodide; (16538-47-9), 66, 61, 62, 66

1-Hexyne; (693-02-7), 66, 66

1-Hexyne, reaction with diisobutylaluminum hydride, 66, 63

Higher order cuprates, 66, 57

HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS, 66, 132

Homoenolate, copper, 66, 47

Homoenolate, titanium, 66, 47

HOMOENOLATE, ZINC, 66, 43

Horner-Wadsworth-Emmons reaction, 66, 220

Hydrazine, 66, 143

Hydrazine, tert-butyl, monohydrochloride, 65, 166

Hydrazine, (1,1-dimethylethyl)-, monohydrochloride, 65, 166

Hydroalumination of alkynes, 66, 64

Hydroboration of alkynes, 66, 64

Hydrogen chloride, 66, 144, 146

Hydrogen peroxide; (7722-84-1), 65, 166

Hydrogen sulfide, 66, 143, 145

Hydroquinone, as diene stabilizer, 66, 63

α -Hydroxylation of ketones, 66, 138

3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE: 1-BUTANONE,
 3-HYDROXY-3-METHYL-1-PHENYL-, (43108-74-3), 65, 6, 12

N-Hydroxymethylphthalimide: Phthalimide, N-(hydroxymethyl)-;
 1H-Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)- (118-29-6), 65, 119

(1-Hydroxy-2-propenyl)trimethylsilane, 66, 14, 15

Hydrozirconation of alkynes, 66, 64

Hypervalent iodine compounds, 66, 138

Imines, reduction by diisobutylaluminum hydride, **66**, 189
 INDOLE, 4-NITRO-, **65**, 146
 INTRAMOLECULAR ACYLATION OF ALKYL SILANES, **66**, 87
 INVERSE ELECTRON DEMAND DIELS-ALDER, **65**, 98
 Iodine, phenylbis(trifluoroacetato-0)-; (2712-78-9), **66**, 141
 Iodobenzene diacetate, **66**, 136
 Iodobenzene dichloride, **66**, 137
 6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine,
 N-[(2-iodo-4,5-dimethoxyphenyl)methylene]-; (61599-78-8), **65**, 108
 o-Iodotoluene; (615-37-2), **66**, 67, 68, 74
 1-Iodo-3-trimethylsilylpropane; (18135-48-3), **66**, 87, 88, 91, 94
 Ion exchange chromatography, **66**, 212, 214, 215
 Iron pentacarbonyl, **66**, 99
 Isobutyl chloroformate, **66**, 135
 (R)-Isobutyloxirane. **66**, 165
 Isoindole-1,3-(2H)-dione, 2-(bromomethyl)-, 1H-, **65**, 119
 Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)-, 1H-, **65**, 119
 (S)-Isoleucine. **66**, 153
 Isomenthol, (+)-: Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2B,5B)]-;
 (23283-97-8), **65**, 81
 Isomenthone, (+)-: Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)-;
 (1196-31-2), **65**, 81
 Isopropyl alcohol, titanium (4+) salt, **65**, 230
 Isopropylideneacetophenone: 2-Buten-1-one, 3-methyl-1-phenyl-;
 (5650-07-7), **65**, 12
 (R)-Isopropyloxirane, **66**, 165

Ketones, preparation from carboxylic acid, **66**, 119

β -Lactams, **65**, 140

Lactic acid, 2-methyl-, methyl ester; (2110-78-3), **66**, 114

Lead dioxide: Lead oxide; (1309-60-0), **65**, 166

Lead oxide, **65**, 166

(S)-Leucine, **66**, 153

Lipshutz reagents, **66**, 57

Lithiobutadiyne, **65**, 52

Lithium, **66**, 127, 128

Lithium aluminum hydride, **66**, 160

Lithium, butyl-, **65**, 98, 108, 119

Lithium diisopropylamide, **65**, 98; **66**, 37, 88, 194

Lithium, methyl-, **65**, 47, 140

Lithium tetrafluoroborate, **66**, 52, 54

Lithium tri(tert-butoxy)aluminum hydride, **66**, 122, 124

Lyophilization, **66**, 212-214

MACROCYCLIC SULFIDES, **65**, 150

Magnesium, **66**, 118, 175

Magnesium ethoxide, **66**, 175

Malonic acid, dimethyl ester; (108-59-8), **66**, 85

Malonic acid, (methoxymethylene)-, dimethyl ester, **65**, 98

Malonic ester alkylation, **66**, 75

Malononitrile, benzylidene-, **65**, 32

p-Mentha-6,8-dien-2-one; (6485-40-1), **66**, 13

p-MENTH-4-(8)-EN-3-ONE, (R)-(+)-, **65**, 203, 215

2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol: Cyclohexanol-2-(1-mercapto-1-methylethyl)-5-methyl-, [1R-(1 α ,2 α ,5 α)]-; (79563-68-1); [1R-(1 α ,2 β ,5 α)]-; (79563-59-0); [1S-(1 α ,2 α ,5 β)]-; (79563-67-0), **65**, 215

Mercury, **66**, 96

Methanamine, N-(phenylmethylene)-, **65**, 140

Methane, dibromo-, **65**, 81

METHANESULFONYL BROMIDE, BROMO-, **65**, 90

Methanesulfonyl chloride; (124-63-0), **66**, 1, 3, 186, 187, 193

Methanethiol, **66**, 188

Methanol; (67-56-1), **66**, 85, 182, 184

N¹N²-Bis(methoxycarbonyl)sulfur diimide: Sulfur diimide, dicarboxy-, dimethyl ester; (16762-82-6), **65**, 159

6-Methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene: 2-Naphthalene-carboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester; (78112-34-2), **65**, 98

Methyl acrylate; (96-33-3), **66**, 54, 59

dimerization by Pd(II), **66**, 52

Methylamine, N-benzylidene-, **65**, 140

METHYL 4-O-BENZOYL-6-BROMO-6-DEOXY- α -D-GLUCOPYRANOSIDE: GLUCOPYRANOSIDE, METHYL 6-BROMO-6-DEOXY, 4-BENZOATE, α -D-; (10368-81-7), **65**, 243

Methyl 4,6-O-benzylidene- α -D-glucopyranoside: Glucopyranoside, methyl 4,6-O-benzylidene- α -D-; α -D-glucopyranoside, methyl 4,6-O-(phenylmethylene)-; (3162-96-7), **65**, 243

N-Methylbenzylideneimine: Methylamine, N-benzylidene-; Methanamine, N-(phenylmethylene)-: (622-29-7), **65**, 140

2-Methyl-2-butene: 2-Butene, 2-methyl-; (513-35-9), **65**, 159

(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester;
(43219-18-7), **66**, 75, 85

(3-Methyl-2-butenyl)(2-propynyl)propanedioic acid, dimethyl ester, **66**, 76

Methyl carbamate: Carbamic acid, methyl ester; (598-55-0), **65**, 159

METHYL 4-CHLORO-2-BUTYNOATE: 2-BUTYNOIC ACID, 4 CHLORO, METHYL ESTER;
(41658-12-2), **65**, 47

Methyl chloroformate: Formic acid, chloro-, methyl ester;
Carbonochloridic acid, methyl ester; (79-22-1), **65**, 47

Methyl (E)-crotonate; (623-43-8), **66**, 38, 39, 41, 42

1-Methylcyclohexene: Cyclohexene, 1-methyl-; (591-49-1), **65**, 90

3-Methyl-2-cyclohexen-1-one; (1193-18-6), **66**, 37, 39, 42

Methyl N,N-dichlorocarbamate: Carbamic acid, dichloro-, methyl ester;
(16487-46-0), **65**, 159

Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate, **66**, 37

Methyl α -D-glucopyranoside: Glucopyranoside, methyl, α -D-;
 α -D-glucopyranoside, methyl; (97-30-3), **65**, 243

4-METHYL-3-HEPTANONE, (S)-(+) -: 3-HEPTANONE, 4-METHYL-, (S)-,
(51532-30-0), **65**, 183

4-Methyl-3-heptanone SAMP-hydrazone, (S)-(+) -: 1-Pyrrolidinamine,
N-(1-ethyl-2-methylpentylidene)-2-(methoxymethyl)-,
[S-[R^{*}, R^{*}-(Z)]-; (69943-24-4), **65**, 183

Methyl 2-hydroxyisobutyrate; (2110-78-3), **66**, 110, 111, 114

Methyl lithium: Lithium, methyl-; (917-54-4), **65**, 47, 140; **66**, 97, 100

Methyl lithium, low halide, **66**, 53, 55

Methylmagnesium chloride, **66**, 1-3

[(Methyl)(methoxy)carbene]pentacarbonyl chromium(0): Chromium,
 pentacarbonyl(1-methoxyethylidene)-, (OC-6-21)-; (20540-69-6), **65**, 140

METHYL N-(2-METHYL-2-BUTENYL)CARBAMATE: CARBAMIC ACID, (2-METHYL-2-BUTENYL)-,
 METHYL ESTER; (86766-65-6), **65**, 159

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (2R,5R)-: Cyclohexanone,
 5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)-;
 (57707-92-3), **65**, 203

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (2S,5R)-: Cyclohexanone,
 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)-; (65337-06-6), **65**, 203

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate, (1R,2S,5R)-:
 Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl
 ester, [1R-(1 α ,2 β ,5 α)]-; (71804-27-8). **65**, 203

5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone, cis- and trans-;
65, 215

5-Methyl-2-(1-methyl-1-thioethyl)cyclohexanol. **65**, 215

N-Methylmorpholine, **66**, 133, 135

2-Methyl-3-nitroaniline: o-Toluidine, 3-nitro-; Benzeneamine,
 2-methyl-3-nitro-; (603-83-8), **65**, 146

2-METHYL-4'-NITROBIPHENYL, **66**, 67, 68

(R)-METHYLOXIRANE; (15448-47-2), **66**, 160, 161, 163, 164, 172

METHYL 6-OXODECANOATE; (61820-00-6), **66**, 116, 117, 120, 123

METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2H-1-BENZOPYRAN-3-CARBOXYLATE:
 2H-1-BENZOPYRAN-3-CARBOXYLIC ACID, 5,6,7,8-TETRAHYDRO-2-OXO-, METHYL
 ESTER; (85531-80-2), **65**, 98

(E)-3-Methyl-3-penten-2-one, **66**, 11

(Z)-3-Methyl-3-penten-2-one, **66**, 11

3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE: 2-CYCLOPENTEN-1-ONE, 3-METHYL-2-PENTYL-; (1128-08-1), **65**, 26

2-METHYL-2-PHENYL-4-PENTENAL: 4-PENTENAL, 2-METHYL-2-PHENYL-; (24401-39-6), **65**, 119

2-Methylpropane-2-thiol; (75-66-1), **66**, 108, 109, 111, 114

Methyl liglate; (6622-76-0), **66**, 88, 91, 94

1-Methyl-1-(trimethylsilyl)allene, **66**, 1, 2, 4

2-METHYL-2-VINYLCYCLOPENTANONE; (88729-76-4), **66**, 87, 88, 90, 91, 94

trans-3-METHYL-2-VINYLCYCLOHEXANONE, **66**, 95, 90

METHYLENATION OF CARBONYL COMPOUNDS, **65**, 81

3-Methylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid, dimethyl ester, **66**, 78

3-METHYLENE-CIS-P-MENTHANE, (+)-: (CYCLOHEXANE, 5-METHYL-1-METHYLENE-2-(1'-METHYLETHYL)-, R,R-), **65**, 81

MICHAEL ADDITION, APROTIC, **66**, 37, 41

cis,cis-Monomethyl muconate; (61186-96-7), **66**, 180, 184

cis,cis-MONOMETHYL MUCONATE FROM 1,2-DIHYDROXYBENZENE, **66**, 180

2-Naphthalenecarboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester, **65**, 98

Nickel-catalyzed aryl-aryl coupling, **66**, 70

4-NITROINDOLE: INDOLE, 4-NITRO-; (4769-97-5), **65**, 146

1-Nitroso-2-methoxymethylpyrrolidine, (S)-: Pyrrolidine, 2-(methoxymethyl)-1-nitroso-, (S)-; (60096-50-6), **65**, 183

Nitrosonium tetrafluoroborate, **66**, 54

Nitroso-tert-octane: Pentane, 2,2,4-trimethyl-4-nitroso-; (31044-98-1), **65**, 166

tert-Octylamine: 2-Pentanamine, 2,4,4-trimethyl-; (107-45-9), **65**, 166

N-tert-Octyl-O-tert-butylhydroxylamine: 2-Pentanamine, N-(1,1-dimethylethoxy)-2,4,4-trimethyl-; (68295-32-9), **65**, 166

1-Octyn-3-ol; (818-72-4), **66**, 22, 23, 28

Organoaluminum compounds, reaction with imino carbocations, **66**, 189

Orthoester Claisen rearrangement, **66**, 22

Orthoformic acid, triethyl ester, **65**, 146

Oxalic acid, diethyl ester, **65**, 146

Oxalyl chloride; (79-37-8), **66**, 15, 17, 21, 89, 94, 117, 121, 123

1,3-OXATHIANE, **65**, 215

Oxaziridine, 3-phenyl-2-(phenylsulfonyl)-; [63160-13-4), **66**, 203, 210

OXIDATIVE CLEAVAGE OF AROMATIC RINGS; **66**, 180

Oximes, mesylation, **66**, 185

Oxirane, methyl; (15448-47-2), **66**, 172

6-OXODECANAL; (63049-53-6), **66**, 121, 122, 126

6-Oxodecanoic acid; (4144-60-9), **66**, 122, 123, 126

Oxonium, trimethyl-, tetrafluoroborate (1-), **65**, 140

(1-OXO-2-PROPENYL)TRIMETHYLSILANE, **66**, 14-16, 18

Ozone (10028-15-6), **65**, 183

Palladium-catalyzed aryl-aryl coupling. **66**. 70

PALLADIUM-CATALYZED COUPLING OF ARYL HALIDES, **66**, 67

Palladium sponge, **66**, 54

Palladium. tetrakis(acetonitrile)-. tetrafluoroborate, **66**, 52

Palladium, tetrakis(triphenylphosphine)-; (14221-01-3),
66, 61, 62, **66**, 68, 69, 74

Paraformaldehyde: Poly(oxymethylene); (9002-81-7), **65**, 215, **66**, 220, 221

1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE: 1,3-CYCLOPENTADIENE, 1,2,3,4,5-PENTAMETHYL-; (4045-44-7), **65**, 42

2-Pentanamine, N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-2,4,4-trimethyl-, **65**, 166

2-Pentanamine, N-(1,1-dimethylethoxy)-2,4,4-trimethyl-, **65**, 166

2-PENTANAMINE, N-(1,1-DIMETHYLETHYL)-2,4,4-TRIMETHYL-, **65**, 166

2-Pentanamine, 2,4,4-trimethyl-, **65**, 166

1,5-PENTANEDIONE, 3,3-DIMETHYL-1,5-DIPHENYL-, **65**, 12

Pentane, 2,2,4-trimethyl-4-nitroso-, **65**, 166

3-Pentanone SAMP-hydrazone: 1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)-; (59983-36-7), **65**, 183

4-PENTENAL, 2-METHYL-2-PHENYL-, **66**, 119

8-PHENYLMENTHOL, (-)-: CYCLOHEXANOL, 5-METHYL-2-(1-METHYL-1-PHENYLETHYL)-, [1R-(1 α ,2 β ,5 α)]-; (65253-04-5), **65**, 203

3-PHENYL-4-PENTENAL, **66**, 29, 31, 36

2-Phenyl-N-(phenylmethylene)-1-propen-1-amine: 1-Propen-1-amine, 2-phenyl-N-(phenylmethylene)-; (64244-34-4), **65**, 119

(E) 3 [(E) 3-Phenyl-2-propenoxy]acrylic acid; (00003-10-5), **66**, 30, 31, 36

(\pm)-trans-2-(PHENYLSULFONYL)-3-PHENYLOXAZIRIDINE, **66**, 203, 204

1-Phenyl-1-trimethylsiloxyethylene: Silane, trimethyl[(1-phenylvinyl)oxy]-; Silane, trimethyl[(1-phenylethenyl)oxy]-; (13735-81-4), **65**, 6

Phosphonate synthesis, **66**, 194

Phosphonic acid, (aminomethyl), diethyl ester, **65**, 119

Phosphonic acid, (diazomethyl)-, dimethyl ester, **65**, 119

Phosphonic acid, diethyl ester; (762-04-9), **66**, 202

Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]-, diethyl ester, **65**, 119

Phosphonic acid, [(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl]-, diethyl ester; (81956-28-7), **66**, 202

Phosphonic acid, (isocyanomethyl)-, diethyl ester, **65**, 119

PHOSPHONIC ACID [(PHENYLMETHYLENE)AMINO]METHYL]-, DIETHYL ESTER, **65**, 119

Phosphonic acid, (phthalimidomethyl)-, diethyl ester, **65**, 119

Phosphoric triamide, hexamethyl-, (680-31-9), **66**, 51, 94

Phosphorodichloridic acid, 2-chloroethyl ester, **65**, 68

Phosphorous acid, triethyl ester, **65**, 108, 119

Phosphorus oxychloride, **66**, 173, 176

Phthalimide, N-(bromoethyl)-, **65**, 119

Phthalimide, N-(hydroxymethyl)-, **65**, 119

PINENE, (-)- α -: 2-PINENE, (1S,5S)-(-); BICYCLO[3.1.1]HEPT-2-ENE, 2,6,6-TRIMETHYL-, (1S)-; (7785-26-4), **65**, 224

PINENE, (-)- β -: BICYCLO[3.1.1]HEPTANE, 6,6-DIMETHYL-2-METHYLENE-, (1S)-; (18172-67-3), **65**, 224

Poly(oxymethylene), **65**, 215

Potassium 3-aminopropylamide (KAPA), **65**, 224

Potassium tert-butoxide, **66**, 127, 128, 195

Potassium hydride; (7693-26-7), **65**, 224

Potassium hydroxide, **66**, 89

Prenyl bromide, **66**, 76

Proline, D-; (344-25-2), **65**, 173

Proline, L-; (147-85-3), **65**, 173

2-Propanamine, N-(1-methylethyl)-, **65**, 98

Propane, 1-bromo-3-chloro-2,2-dimethoxy-, **65**, 32

Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E)-, **65**, 68

Propane, 2,2'-[(1,2-dichloro-1,2-ethanediyl)]bis(oxy)bis[2-methyl-,
(R*,R*)-(±)-, 65, 68

Propane, 2,2'-[(1,2-dichloro-1,2-ethanediyl)]bis(oxy)]bis[2-methyl-,
(R*,S*)-, 65, 68

PROPANE, 2,2'-[1,2-ETHYNYLEDIYL BIS (OXY)] BIS [2-METHYL-, 65, 68

1,3-Propanediamine; (109-76-2), 65, 224; 66, 131

Propanedinitrile, (phenylmethylene)-, 65, 32

Propanedioic acid, (cyclopropylcarbonyl)-, diethyl ester;
(7394-16-3), 66, 179

Propanedioic acid, diethyl ester; (105-53-3), 66, 179

Propanedioic acid, (methoxymethylene)-, dimethyl ester, 65, 98

Propanedioic acid, (3-methyl-2-butenyl)-, dimethyl ester;
(43219-18-7), 66, 85

1,3-Propanediol; (504-63-2), 65, 32

1,3-Propanedithiol; (109-80-8), 65, 150

2-Propanethiol, 2-methyl-; (75-66-1), 66, 114

1-Propanol, 2-chloro-, (S)-(+)-; (19210-21-0), 66, 172

Propanoic acid, 2-chloro-, (S)-; (29617-66-1), 66, 159, 172

Propanoic acid, 2-hydroxy-2-methyl-, methyl ester; (2110-78-3), 66, 114

2-Propanol, titanium (4+) salt, 65, 230

2-Propanone, 1-bromo-3-chloro-, dimethyl acetal, 65, 32

Propargyl bromide; (106-96-7), 66, 77, 79, 86

PROPARGYL CHLORIDE: PROPYNE, 3-CHLORO-; 1-PROPYNE, 3-CHLORO-;
(624-65-7), 65, 47

1-Propen-1-amine, 1-chloro-N,N,2-trimethyl-; (26189-59-3), 66, 120

1-Propen-1-amine, 2-phenyl-N-(phenylmethylene)-, 65, 119

2-Propenenitrile, 65, 236

2-Propenoic acid, 2-(bromomethyl)-, ethyl ester; (17435-72-2), **66**, 224

2-Propenoic acid, 2-(hydroxymethyl)-, ethyl ester; (10029-04-6), **66**, 224

2-Propen-1-ol; (107-18-6), **66**, 21

2-Propen-1-ol, 1-(trimethylsilyl)-; (95061-68-0), **66**, 21

2-Propyl-1-azacycloheptane; (85028-29-1), **66**, 186-188, 193

2-PROPYL-1-AZACYCLOHEPTANE FROM CYCLOHEXANONE OXIME, **66**, 185

Propylene oxide, (R)-(+)-; (15448-47-2), **66**, 172

Propyne, 3-bromo-; (106-96-7), **66**, 86

1-PROPYNE, 3 CHLORO-, **65**, 47

2-Propyn-1-ol, 3-(trimethylsilyl)-; (5272-36-6), **66**, 7

2-Propyn-1-ol, silylation of, **66**, 3

Protodestannylation, **66**, 77, 78, 80

PULEGONE, (+): p-MENTH-4-(8)-EN-3-ONE, (R)-(+)-; CYCLOHEXANONE, 5-METHYL-2-(1-METHYLETHYLIDENE)-, (R)-; (89-82-7), **65**, 203, 215

4-Pyridinamine, N,N-dimethyl-, **65**, 12

Pyridine, **66**, 180, 182

Pyridine, 4-(dimethylamino)-, **65**, 12

2(1H)-Pyrimidone, tetrahydro-1,3-dimethyl-; (7226-23-5), **66**, 94

Pyrocatechol; (120-80-9), **66**, 184

Pyrophosphoric acid, disodium salt; (7758-16-9), **66**, 219

1-Pyrrolidinamine, N-(1-ethyl-2-methylpentylidene)-2-(methoxymethyl)-, [S-[R*,R*-(Z)]-, **65**, 183

1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)-, **65**, 183

1-Pyrrolidinamine, 2-(methoxymethyl)-, (R)-(+)-; (72748-99-3), **65**, 173

1-Pyrrolidinamine, 2-(methoxymethyl)-, (S)-(-)-; (59983-30-0), **65**, 173, 183

Pyrrolidine, 2-(methoxymethyl)-, (S)-(+)-; (63126-47-6), **65**, 173

Pyrrolidine, 2-(methoxymethyl)-1-nitroso-, (S)-, **65**, 183

1-Pyrrolidinecarboxaldehyde, 2-(hydroxymethyl)-, (S)-(-)-; (55456-46-7),
65, 173

1-Pyrrolidinecarboxaldehyde, 2-(methoxymethyl)-, (S)-(-)-; (63126-45-4),
65, 173

2,5-PYRROLIDINEDIONE, 1-BROMO-, **65**, 243

2-Pyrrolidinemethanol, (S)-(+)-; (23356-96-9), **65**, 173

2-Pyrrolidinone, 1-vinyl-, (88-12-0), **66**, 149

RADICAL CYCLIZATION, **66**, 75

Ramberg-Bäcklund reaction, **65**, 90

RAMP: (R)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine,
 2-(methoxymethyl)-, (R)-; **65**, 173, 103

REDUCTION OF CARBOXYLIC ACIDS TO ALDEHYDES, **66**, 121

RING EXPANSION, **65**, 17

of cyclic ketoximes, **66**, 189

SAMP: (S)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine,
 2-(methoxymethyl)-, (S)-; (59983-39-0), **65**, 173, 183

SILANE, 1,3-BUTADIENE-1,4-DIYLBIS[TRIMETHYL-, **65**, 52

Silane, (3-chloropropyl)trimethyl-, (2344-83-4), **66**, 94

Silane, chlorotrimethyl-, **65**, 61, 1; **66**, 21, 44

Silane, (1-cyclobuten-1,2-ylenedioxy)bis[trimethyl-, **65**, 17

Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl-, **65**, 17

Silane, [(1-ethoxycyclopropyl)oxy]trimethyl-, (27374-25-0), **66**, 51

Silane, ethynyltrimethyl-, **65**, 52, 61

Silane, (3-iodopropyl)trimethyl-, (18135-48-3), **66**, 94

SILANE. (ISOPROPENYLOXY)TRIMETHYL-, **65**, 1

SILANE, TRIMETHYL[(1-METHYLETHENYL)OXY]-, **65**, 1

Silane, trimethyl(1-methyl-1,2-propadienyl)-; (74542-82-8), **66**, 7, 13

SILANE, TRIMETHYL(1-OXO-2-PROPENYL)-; (51023-60-0), **66**, 14, 21

Silane, trimethyl[(1-phenylethyl)oxy]-, **65**, 6, 12

Silane, trimethyl[(1-phenylvinyl)oxy]-, **65**, 6, 12

Silver nitrate, **66**, 111

 reaction with 1-trimethylsilyl-1-butene, **66**, 4

Silver(I) oxide; (20667-12-3), **66**, 111, 115

Silver(I) trifluoroacetate; (2966-50-9), **66**, 115

 preparation, **66**, 111

Sodium; (7440-23-5), **66**, 76, 85, 96

Sodium amalgam, **66**, 96

Sodium dicarbonyl(cyclopentadienyl)ferrate; (12152-20-4), **66**, 96, 107

Sodium fluoride, aqueous, work-up for organoaluminum reactions, **66**, 188

Sodium hydride; (7646-69-7), **66**, 30, 32, 76, 79, 85, 109, 111, 114

Sodium iodide, **66**, 87

Sodium methoxide, **66**, 76

Sodium naphthalenide, **65**, 166

Sodium nitrite, **66**, 151

Sodium tungstate dihydrate: Tungstic acid, disodium salt, dihydrate;
 (10213-10-2), **65**, 166

Sonication, for reaction of 1,3-diaminopropane with alkali metals, **66**, 130

SPIRO[4.5]DECAN-1,4-DIONE; (39984-92-4), **65**, 17

Stannane, tetrachloro-, **65**, 17

Stannane, tributyl-, **65**, 236

STETTER REACTION, **65**, 26

SUCCINIMIDE, N-BROMO-, **65**, 243

2-Sulfonyloxaziridines, preparation, **66**, 207, 208

Sulfosalicylic acid spray for tlc plates, **66**, 216

Sulfur chloride, **65**, 159

Sulfur dichloride: Sulfur chloride; (10545-99-0), **65**, 159

Sulfur diimide, dicarboxy-, dimethyl ester, **65**, 159

Sulfuryl chloride isocyanate, **65**, 135

Swern oxidation, **6**, 15, 18

2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide: Glucopyranosyl bromide tetraacetate, α -D-; α -D-glucopyranosyl bromide, 2,3,4,6-tetraacetate; (572-09-8), **65**, 236

Tetrabutylammonium fluoride; (429-41-4), **66**, 110, 111, 115

Tetrabutylammonium hydroxide; (2052-49-5), **66**, 214, 219

Tetrafluoroboric acid-diethyl ether complex; (67969-82-8),
66, 97, 98, 100, 107

Tetraisopropyl titanate: Isopropyl alcohol, titanium (4+) salt;
2-Propanol, titanium (4+) salt; (546-68-9), **65**, 230

Tetrakis(acetonitrile)palladium tetrafluoroborate; (21797-13-7),
66, 52, 54, 59

Tetrakis(triphenylphosphine)palladium; (14221-01-3),
66, 61, 62, 66, 68, 69, 74

4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE:
[1,1'-BIPHENYL]-2,2'-DICARBOXALDEHYDE, 4,4',5,5'-TETRAMETHOXY-;
(29237-14-7), **65**, 108

Tetramethyltin, **66**, 55

2,5,7,10-Tetraoxabicyclo[4.4.0]decane, cis-: p-Dioxino[2,3,-b]-p-dioxin,
 hexahydro-; [1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro;
 (4362-05-4), **65**, 68

1,4,8,11-TETRATHIACYCLOTETRADECANE; (24194-61-4), **65**, 150

Tetravinyltin, **66**, 53, 55

Tetronic acids, **66**, 111, 112

Thiourea: Urea, thio-; (62-56-6), **65**, 150

Tin chloride, **65**, 17

Tin tetrachloride: Tin chloride; Stannane, tetrachloro-; (7646-78-8), **65**, 17

Tin, tetramethyl-, **66**, 55

Tin, tetravinyl-, **66**, 53, 55

Titanium chloride, **65**, 81, 6

Titanium tetrachloride: Titanium chloride; (7550-45-0), **65**, 81, 6;
66, 8, 9

Toluene, o-Iodo-; (615-37-2), **66**, 74

α -Toluenethiol, **65**, 215

o-Toluidine, 3-nitro-, **65**, 146

o-Tolyl lithium, preparation, **66**, 69

o-Tolylzinc chloride; (84109-17-1), **66**, 67, 74

Transesterification, **65**, 230

1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester;
 (74476-38-3), **66**, 149

1,2,4-Triazines, as Diels-Alder dienes, **66**, 147, 148

Tributylamine, **66**, 173, 176

(Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic
 acid, dimethyl ester, **66**, 77

Tributyltin hydride: Stannane, tributyl-, (688-73-3), **65**, 236;
66, 77, 79, 86

2,3,6-Tricarboethoxypyridine, **66**, 145

Triethylamine, **66**, 15, 16, 174, 176, 185

Triethyl orthoacetate; (78-39-7), **66**, 22, 23, 28

Triethyl orthoformate: Orthoformic acid, triethyl ester; Ethane,
 1,1',1"-[methylidynetris(oxy)]tris-, (122-51-0), **65**, 146

Triethyl phosphite: Phosphorous acid, triethyl ester; (122-52-1),
65, 119, 108

Triethyl phosphonoacetate; (867-13-0), **66**, 220, 224

TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE; (74476-38-3),
66, 142, 144, 145, 149

Trifluoroacetic acid; (76-05-1), **66**, 111, 115, 136

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride;
 (40/-25-0), **65**, 12; **66**, 153

[I,I-BIS(TRIFLUOROACETOXY)]IODOBENZENE, **66**, 132, 134, 136, 141

Trimethylamine, **66**, 29, 32

2,2,6-Trimethyl-1,3-dioxen-4-one; (5394-63-8), **66**, 195, 196, 202

3,4,5-Trimethyl-2,5-heptadien-4-ol: 2,5-Heptadien-4-ol, 3,4,5-trimethyl
 (64417-15-8), **65**, 42

Trimethyloxonium tetrafluoroborate: Oxonium, trimethyl-, tetrafluoroborate
 (1-); (420-37-1), **65**, 140

TRIMETHYLSILYLACETYLENE: SILANE, ETHYNYLTRIMETHYL-, (1066-54-2), **65**, 52, 61

1-Trimethylsilyloxy-1-ethoxycyclopropane, **66**, 44

3-Trimethylsilyl-2-propyn-1-ol, **66**, 1, 3

3-Trimethylsilyl-2-propyn-1-yl methanesulfonate, **66**, 2

Tripropylaluminum; (102-67-0), **66**, 186, 188, 193

Tris(tetrabutylammonium) hydrogen pyrophosphate trihydrate;
(76947-02-9), **66**, 212, 219

Trithiane. Sym-: S-Trithiane; 1.3.5-Trithiane; (291-21-4), **65**, 90

Tungstic acid, disodium salt, dihydrate, **65**, 166

ULLMANN REACTION, **65**, 108

2,5-Undecanedione; (7018-92-0), **65**, 26

Urea, thio-, **65**, 150

(S)-Valine, **66**, 153

Vilsmeier-Haack reagent, **66**, 121

Vibro-mixer, **65**, 52

Vinyl acetate: Acetic acid vinyl ester; Acetic acid ethenyl ester;
(108-05-4), **65**, 135

VINYL CATION EQUIVALENT, **66**, 95

Vinyl cation synthons, **66**, 102

Vinyl radical cyclization, **66**, 81, 82

VINYLATION OF ENOLATES, **66**, 95, 104

Vinyl lithium, **66**, 53, 55

N-Vinyl-2-pyrrolidone; (88-12-0), **66**, 145, 146, 149

Volatile reaction products, apparatus for collecting, **66**, 161, 162

Wittig rearrangement, **66**, 19

Zinc chloride; (7646-85-7), **66**, 43, 45, 51, 61, 62, 68, 69

ZINC HOMOENOLATE, **66**, 43

Zinc, chloro(2-methylphenyl)-; (84109-17-1), **66**, 74

Zipper reaction, alkyne isomerization, **66**, 129

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AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS
VOLUME 67
1988

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society, The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60-64 are being incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which will appear as *Collective Volume Seven* in the traditional hard cover format. It will be available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendices. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is adopted. For example, both diethyl ether and ethyl ether are normally used. Since ethyl ether is the established *Chemical Abstracts* name for the 8th Collective Index, it has been used in this volume. The 9th Collective Index name is 1,1'-oxybisethane, which the Editors consider too cumbersome.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Tear-out copies of this form may be found at the back of this volume. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

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- 1) Authors
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Submit to: Dr. Jeremiah P. Freeman, Secretary
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Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of E. I. du Pont de Nemours and Co., Inc., Hoffmann-La Roche, Inc., and the Rohm and Haas Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

PREFACE

This volume contains 30 reliable preparations that demonstrate new general synthetic methods or provide specific compounds of broad interest to synthetic chemists. The synthesis of chiral molecules and the use of organometallic reagents are again emphasized in this annual volume. The first part comprises procedures for making various optically pure materials, including some binaphthyl derivatives that have proved to be among the most useful chiral auxiliaries for asymmetric synthesis. It opens with Jacques and Fouquey's preparation of 1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE enantiomers, followed by Truesdale's procedure for converting one of them to (R)-(+)-1,1'-BINAPHTHALENE-2,2'-DIOL. Next is Noyori's route to both optically pure enantiomers of BINAP. The effectiveness of BINAP as a ligand for metal-catalyzed asymmetric reactions is amply illustrated by the accompanying procedure for making (R)-(-)-N,N-DIETHYL-(E)-CITRONELLAENAMINE AND (R)-(+)-CITRONELLAL via the Rh(I)-catalyzed asymmetric isomerization of N,N-DIETHYLGERANYLAMINE or N,N-DIETHYLNERYLAMINE. A new chiral auxiliary for activating secondary amines toward metallation and alkylation is (S)-N,N-DIMETHYL-N'-(1-tert-BUTOXY-3-METHYL-2-BUTYL)FORMAMIDINE, and its use in asymmetric methylation is nicely demonstrated in the preparation of (-)-SALSOLIDINE. An improved synthesis of the chiral synthon N-tert-BUTOXYCARBONYL-L-LEUCINAL is described next, and the final procedure in this part, CONDENSATION OF (-)-DIMETHYL SUCCINATE DIANION WITH 1,ω-DIHALIDES, presents a general method for making optically active trans-cycloalkane-1,2-dicarboxylic acids.

The next 15 procedures illustrate the diverse uses of metallic reagents to promote synthetically useful transformations. The first five involve Pd catalysis, beginning with the preparations of **ETHYL (E)-4-(4-NITROPHENYL)-4-OXO-2-BUTENOATE** and **ETHYL 5-OXO-6-METHYL-6-HEPTENOATE** which entail Pd(0)-catalyzed couplings of acid chlorides with organotin and organozinc reagents, respectively. Next are examples of **1,4-FUNCTIONALIZATION OF 1,3-DIENES VIA PALLADIUM-CATALYZED CHLOROACETOXYLATION AND ALLYLIC AMINATION** and **PALLADIUM(0)-CATALYZED syn-1,4-ADDITION OF CARBOXYLIC ACIDS TO CYCLOPENTADIENE MONOEPoxide**, followed by the two-step preparation of **4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE**, which employs a Pd(II)-Cu(I) catalyzed oxidation of 2,2-dimethyl-4-pentenal to 2,2-dimethyl-4-oxopentanal in the first step.

Organosilicon reagents play a key role in each of the next five procedures. The synthesis of **2-METHYL-2-UNDECENE FROM ETHYL DECANOATE** demonstrates the use of α -(diphenylmethylsilyl)esters as vinyl cation equivalents, and **N-BENZYL-N-METHOXYMETHYL-N-(TRIMETHYLSILYL)METHYLAMINE** is shown in the next procedure to be an effective azomethine ylide equivalent. The reaction of trimethylsilylenol ethers with hexacarbonyl(propargylum)-dicobalt salts provides a general method for α -propargylation of ketones, which is exemplified by the synthesis of **2-(1-METHYL-2-PROPYNYL)CYCLOHEXANONE** from cyclohexanone. Finally, Paquette makes use of an aluminum chloride promoted reaction between bis(trimethylsilyl)acetylene and p-toluenesulfonyl chloride in his synthesis of **ETHYNYL p-TOLYL SULFONE**, which is a useful Michael acceptor and acetylene synthon in Diels-Alder reactions.

This section of the volume concludes with procedures involving the elements Se, Ni, Al, Ti, and Rh. Paquette's method for dienophile activation via selenosulfonation is illustrated by the preparation of 1-(BENZENE-SULFONYL)CYCLOPENTENE, and the accompanying preparation of BICYCLO[4.3.0]NON-1-EN-4-ONE gives an example of the versatile use of such α,β -unsaturated sulfone dienophiles. Nickel(II) is used as a catalyst in the procedure to make ETHYL α -(HEXAHYDROAZEPINYLDENE-2)-ACETATE FROM O-METHYLCAPROLACTAM AND MELDRUM'S ACID, which is a specific example of a general route to cyclic β -enamino methyl and ethyl esters. The next procedure uses a combination of tri-iso-butyl aluminum and diiodomethane to effect the SELECTIVE CYCLOPROPANATION OF (S)-(-)-PERILLYL ALCOHOL. This new method is notable for its regioselectivity, which differs from that of the traditional Simmons-Smith cyclopropanation reaction or its modifications. Seebach's synthesis of 3'-NITRO-1-PHENYLETHANOL BY ADDITION OF METHYLTRIISOPROPOXYTITANIUM TO m-NITROBENZALDEHYDE elegantly illustrates the selectivity of this organotitanium reagent for carbonyl groups. This section concludes with an interesting synthesis of N-ACETYL-N-PHENYLHYDROXYLAMINE VIA CATALYTIC TRANSFER HYDROGENATION OF NITROBENZENE USING HYDRAZINE AND RHODIUM ON CARBON.

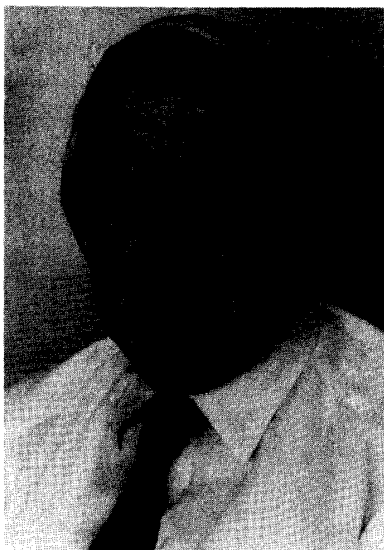
Four of the last five entries in this volume are convenient procedures to make functionalized molecules that are useful precursors to more complex structures: METHYL 7-HYDROXYHEPT-5-ENOATE and 4-METHOXY-3-PENTEN-2-ONE, both of which, for example, are used in making prostaglandins; 3-HYDROXY-1-CYCLOHEXENE-1-CARBOXALDEHYDE; and (E)-2-(1-PROPENYL)CYCLOBUTANONE. The final procedure describes a remarkably selective 4-CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS by N-chlorodialkyl amines.

I wish to thank Dr. Theodora W. Greene for her conscientious editorial assistance and especially Professor Jeremiah P. Freeman, our indefatigable Secretary, for his help in preparing the text and structures for this volume. All of the structures were drawn using the ChemDraw™ program. I also am grateful to my colleagues on the Editorial Board who made my tenure such an enjoyable and rewarding experience.

Wilmington, Delaware

Bruce E. Smart

July 1988



CARL SHIPP MARVEL

September 11, 1894 - January 4, 1988

Carl S. Marvel had a spectacular career of 72 years in organic chemistry. From 1920 to 1961 he was on the staff of the University of Illinois and from the date of his first retirement through 1987, he was a faculty member at the University of Arizona. He consulted for nearly 60 years for the DuPont Company. He was a dominant figure in American organic chemistry and has been recognized as the "father" of synthetic polymer

chemistry. His early contributions to *Organic Syntheses* are easily recognizable by perusal of Collective Volume I of this series, which contained the preparations that appeared in the first nine annual volumes, was published in 1932, and was reprinted in 1941. Nearly 20% of the 264 preps in that collective volume were either submitted by Marvel or checked by him. It was Marvel's experience with the "summer preps" group, or - more formally - "Organic Chemical Manufactures", at the University of Illinois starting in 1916, plus his provision and checking of preps for *Organic Syntheses*, that gave him wide-ranging synthetic experience.

Born on a farm near Waynesville, Illinois, Carl Marvel attended a one-room grammar school and then Waynesville Academy, where he thrived on Latin and Greek. He was introduced to chemistry as a freshman at Illinois Wesleyan University in 1911. An uncle who had been a high school teacher advised his nephew to take this subject if he expected to be a farmer, since the next generation of farmers was going to require scientific knowledge to get the most out of their work. At Illinois Wesleyan, Carl Marvel found enjoyment in organic chemistry and was delighted to learn from his professor, Alfred W. Homberger, that he could be paid to study further, by means of a \$250 scholarship, at the University of Illinois. His graduate education in 1915 started with an overload of course work, including four lab courses, in order to "catch up". When he was not studying, he worked late at night in the laboratory. As a result, he slept as late as possible but still got to the breakfast table before the dining room door closed at 7:30 a.m. His student colleagues decided that was the only time he ever hurried, and they nicknamed him "Speed". A nickname was appropriate to his friendly spirit, but it causes us to smile because it was really an accurate moniker indicative of his chemical thinking, his human insight, his fishing and bird-watching prowess,

and the alacrity with which he found out how he could help a student or colleague with a chemical or personal problem.

We all know from the literature after 1920 and from his many award citations what followed in Speed Marvel's research when he joined the faculty of the University of Illinois, starting with synthesis as the initial motivation and moving boldly into areas of rearrangements, free radical chemistry and magnetic susceptibility, hydrogen bonding, stereoisomerism, structure of organo-mercury and phosphorus compounds, and - most important of all - polymers. While he always felt, and often reminded his colleagues, that the essential product of academic research was the students, he also taught that the best graduate training was to be achieved, along with possible national prestige, by work on essential problems. He believed that there was no such thing as a dead end to a worthwhile problem - delays and detours and retracing of steps, indeed, but no dead end. His research on polymers started with the peroxide-initiated reaction of sulfur dioxide with olefins. He then became interested in the basic mechanism of vinyl polymerization and how vinyl units went together to form a polymer. His research contributions to synthetic rubber, initiated during the second world war under the auspices of the National Defense Research Council and lasting into the mid-50's, together with the findings of his technical intelligence mission after the war, had a lasting impact on the American rubber industry. Marvel's association with the U.S. Air Force research program began toward the end of his first career at the University of Illinois and continued throughout his entire second career at the University of Arizona. During a 30-year period he was the principal contributor to the Air Force program on high temperature polymer synthesis. His basic research led to the commercialization of polybenzimidazole (PBI)

which, because of its exceptional resistance to fire, is used in the suits of astronauts and fire fighters.

Speed Marvel was a founder of the High Polymer Forum that became the Division of Polymer Chemistry of the American Chemical Society, of which he became Chairman in 1950-1951. During his 74-year membership in the ACS, he held just about every elective office possible up to and including the presidency in 1945. The all-purpose meeting room of the ACS building in Washington, D.C. is designated "Marvel Hall" to indicate the esteem with which the ACS held Speed Marvel and the Society's gratitude for the leadership he provided in raising the funds that made the building possible. During his long career he gave unselfishly of his time on a variety of committees and editorial boards, as he did also for his two Universities. Both Arizona and Illinois have annual Marvel Lectureships and Marvel Scholarships. In 1984, the University of Arizona renamed the chemistry laboratory building where he worked the Carl S. Marvel Laboratories of Chemistry.

Honors in steady stream were awarded to Marvel during his career, culminating in the Distinguished Service Award from the U.S. Air Force Materials Laboratory and the National Medal of Science. Other awards included the Nichols, Gibbs, Priestley, and Perkin Medals and election to the Plastics Hall of Fame.

Speed will long be remembered by every chemist who came in contact with him. His students, colleagues, and fellow members of the Boards of *Organic Syntheses* will particularly cherish his memory. He has left us a legacy we can all appreciate.

April 21, 1988

Nelson J. Leonard

CONTENTS

J. Jacques and C. Fouquey	1	ENANTIOMERIC (S)-(+)- AND (R)-(-)-1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE
Larry K. Truesdale	13	(R)-(+)-1,1'-BINAPHTHALENE-2,2'-DIOL
Hidemasa Takaya, Susumu Akutagawa, and Ryoji Noyori	20	(R)-(+)- AND (S)-(-)-2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL (BINAP)
Kazuhide Tani, Tsuneaki Yamagata, Sei Otsuka, Hidenori Kumabayashi, and Susumu Akutagawa	33	(R)-(-)-N,N-DIETHYL-(E)-CITRONELLAENAMINE AND (R)-(+)-CITRONELLAL VIA ISOMERIZATION OF N,N-DIETHYLGERANYLAMINE OR N,N-DIETHYLNERYLAMINE
Kunihiko Takabe, Takashi Katagiri, Juntaro Tanaka, Tsutomu Fujita, Shoji Watanabe, and Kyoichi Suga	44	ADDITION OF DIALKYLAMINES TO MYRCENE: N,N-DIETHYLGERANYLAMINE
Kunihiko Takabe, Takashi Yamada, Takao Katagiri, and Juntaro Tanaka	48	TELOMERIZATION OF ISOPRENE WITH DIALKYLAMINE: N,N-DIETHYLNERYLAMINE
Daniel A. Dickman, Michael Boes, and Albert I. Meyers	52	(S)-N,N-DIMETHYL-N'(1-tert-BUTOXY-3-METHYL-2-BUTYL)FORMAMIDINE
Albert I. Meyers, Michael Boes, and Daniel A. Dickman	60	(-)-SALSOLIDINE
O. P. Goel, U. Krolls, M. Stier, and S. Kesten	69	N-tert-BUTOXYCARBONYL-L-LEUCINAL
Kyoji Furuta, Kiyoshi Iwanaga, and Hisashi Yamamoto	76	CONDENSATION OF (-)-DIMETHYL SUCCINATE DIANION WITH 1, ω -DIHALIDES: (+)-(1S,2S)-CYCLOPROPANE-1,2-DICARBOXYLIC ACID
A. F. Renaldo, J. W. Labadie, and J. K. Stille	86	PALLADIUM-CATALYZED COUPLING OF ACID CHLORIDES WITH ORGANOTIN REAGENTS: ETHYL (E)-4-(4-NITRO-PHENYL)-4-OXO-2-BUTENOATE
Yoshinao Tamaru, Hirofumi Ochiai, Tatsuya Nakamura, and Zen-ichi Yoshida	98	ETHYL 5-OXO-6-METHYL-6-HEPTENOATE FROM METHACRYLOYL CHLORIDE AND ETHYL 4-IODOBUTYRATE

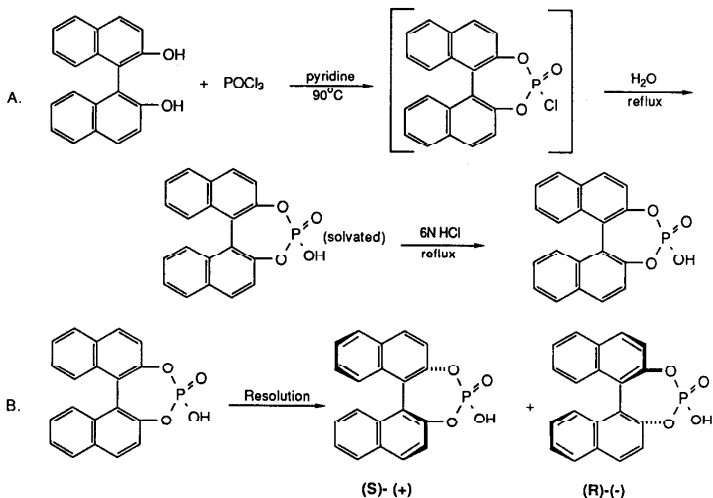
J. E. Nyström, T. Rein, and J. E. Bäckvall	105	1,4-FUNCTIONALIZATION OF 1,3-DIENES VIA PALLADIUM-CATALYZED CHLORO- ACETOXYLATION AND ALLYLIC AMINATION: 1-ACETOXY-4- DIETHYLAMINO-2-BUTENE AND 1- ACETOXY-4-BENZYLAMINO-2-BUTENE
Donald R. Deardorff and David C. Myles	114	PALLADIUM(0)-CATALYZED <i>syn</i> -1,4- ADDITION OF CARBOXYLIC ACIDS TO CYCLOPENTADIENE MONOEPOXIDE: <i>cis</i> - 3-ACETOXY-5-HYDROXYCYCLOPENT-1-ENE
David Pauley, Frank Anderson, and Tomas Hudlicky	121	4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE
Gerald L. Larson, Ingrid Montes de Lopez-Cepero, and Luis Rodriguez Miele	125	α -DIPHENYLMETHYLSILYLATION OF ESTER ENOLATES: 2-METHYL-2-UNDECENE FROM ETHYL DECANOATE
Albert Padwa and William Dent	133	N-BENZYL-N-METHOXYMETHYL-N- (TRIMETHYLSILYL)METHYLAMINE AS AN AZOMETHINE YLIDE EQUIVALENT: 2,6-DIOXO-1-PHENYL-4-BENZYL-1,4- DIAZABICYCLO[3.3.0]OCTANE
Valsamma Varghese, Manasi Saha, and Kenneth M. Nicholas	141	ALKYLATIONS USING HEXACARBONYL- (PROPARGYLIUM)DICOBALT SALTS: 2-(1-METHYL-2-PROPYNYL)- CYCLOHEXANONE
Liladhar Waykole and Leo A. Paquette	149	ETHYNYL <i>p</i> -TOLYL SULFONE
Ho-Shen Lin, Michael J. Coghlan, and Leo A. Paquette	157	DIENOPHILE ACTIVATION VIA SELENOSULFONATION: 1-(BENZENESULFONYL)CYCLOPENTENE
Ho-Shen Lin and Leo A. Paquette	163	REDUCTIVE ANNULATION OF VINYL SULFONES: BICYCLO[4.3.0]NON- 1-EN-4-ONE
J. P. Celerier, E. Deloisy-Marchalant, G. Lhomme, and P. Maitte	170	ETHYL α -(HEXAHYDROAZEPINYLIDENE)-2)- ACETATE FROM O-METHYLCAPROLACTAM AND MELDRUM'S ACID
Keiji Maruoka, Soichi Sakane, and Hisashi Yamamoto	176	SELECTIVE CYCLOPROPANATION OF (S)-(-)-PERILLYL ALCOHOL: 1-HYDROXYMETHYL-4-(1-METHYLCYCLO- PROPYL)-1-CYCLOHEXENE
René Imwinkelried and Dieter Seebach	180	3'-NITRO-1-PHENYLETHANOL BY ADDITION OF METHYLTRIISOPROPOXY- TITANIUM TO <i>m</i> -NITROBENZALDEHYDE

P. W. Oxley, B. M. Adger, M. J. Sasse, and M. A. Forth	187	N-ACETYL-N-PHENYLHYDROXYLAMINE VIA CATALYTIC TRANSFER HYDROGENATION OF NITROBENZENE USING HYDRAZINE AND RHODIUM ON CARBON
Guy Casy, John W. Patterson, and Richard J. K. Taylor	193	METHYL 7-HYDROXYHEPT-5-ENOATE
George A. Kraus, Michael E. Krolski, and James Sy	202	4-METHOXY-3-PENTEN-2-ONE
H. L. Rigby, M. Neveu, D. Pauley, B. C. Ranu, and T. Hudlicky	205	3-HYDROXY-1-CYCLOHEXENE-1- CARBOXALDEHYDE
Scott A. Miller and Robert C. Gadwood	210	SYNTHESIS OF CYCLOBUTANONES VIA 1-BROMO-1-ETHOXYCYCLOPROPANE: (E)-2-(1-PROPENYL)CYCLOBUTANONE
John R. Lindsay Smith, Linda C. McKeer, and Jonathan M. Taylor	222	4-CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS: 2,4-DICHLOROMETHOXYBENZENE
Unchecked Procedures	232	

ENANTIOMERIC (S)-(+)- AND (R)-(-)-

1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE

(Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin, 4-hydroxy-, 4-oxide)



Submitted by J. Jacques and C. Fouquey.¹

Checked by P. R. Carlier and K. Barry Sharpless.

1. Procedure

Caution! Part A of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (pyridine, phosphorus oxychloride).

A. *(±)-Binaphthylphosphoric (BNP) acid.* A 1-L, three-necked flask, fitted with a magnetic stirring bar, pressure-equalizing dropping funnel, reflux condenser topped by a calcium chloride drying tube, and a thermometer, is charged with 450 mL of pyridine and, while stirring, with 100 g (0.35 mol) of *(±)-1,1'-bi-2-naphthol* (Note 1).

To this stirred suspension, 73.6 g (0.48 mol) of freshly distilled phosphorus oxychloride is added dropwise, whereupon the temperature rises to about 80°C, most of the binaphthol dissolves, and pyridine hydrochloride crystals form. Complete dissolution is achieved by heating to 90°C. The stirred solution is allowed to cool to 50-60°C (crystallization occurs at about 85°C). To the stirred suspension, 40 mL of water is added dropwise (*Caution, exothermic reaction!*), which raises the temperature to the boiling point (ca. 118°C). The resulting solution, cooled to about 60°C, is transferred to a 1-L dropping funnel and the flask is rinsed with pyridine (2 x 20 mL). The solution and rinse are combined and added dropwise with vigorous stirring to 900 mL of 6 N hydrochloric acid (Note 2), which gives a precipitate of pyridine-solvated binaphthylphosphoric (BNP) acid (Note 3). This crude product is collected by suction filtration. The wet cake is transferred to a 2-L, large-necked flask and stirred with 300 mL of 6 N hydrochloric acid. The suspension is heated to boiling (possible foaming!) and immediately cooled. The solid is thoroughly filtered by suction, washed twice with 20 mL of water (Note 4), and air-dried to afford 114-119 g (94-99%) of *(±)-binaphthylphosphoric acid*. This compound, which decomposes without

melting at about 300°C (Note 5), is pure enough to be resolved. Analytical crystalline samples can be obtained from ethanol.

B. (S)-(+)- and (R)-(-)-BNP acid. In a 2-L flask 95.2 g (0.27 mol) of racemic binaphthylphosphoric (BNP) acid and 80.4 g (0.27 mol) of (+)-cinchonine (Note 6) are dissolved in 985 mL of hot methanol (Note 7). To the hot (65°C) solution is added 420 mL of hot water via a dropping funnel over the course of 20 min. *During the addition the solution is vigorously stirred and maintained at 65-70°C. At the end of the addition, the flask is transferred to another (cool) stirring plate. Crystallization starts at approximately 60°C, and stirring is maintained until the solution has reached room temperature* (Note 8). The crystals are collected, washed with a 2:1 methanol-water mixture (3 x 45 mL) and air dried to afford 76.6 g of salt consisting of 91% p salt [(+)-acid, (+)-base] and 9% n salt [(-)-acid, (+)-base], $[\alpha]_{546}^{25} +424^\circ$ (methanol, c 0.99) (Notes 9 and 10).

(S)-(+)-BNP acid. A 2-L, three-necked flask, equipped with addition funnel, reflux condenser, magnetic stirring bar, and thermometer, is charged with 76.6 g of the above salt and 500 mL of ethanol. The salt is dissolved by heating to reflux, and 570 mL of 6 N hydrochloric acid is added with vigorous stirring over the course of 30 min. The temperature is maintained between 75-80°C during the addition, and the acid begins to precipitate. Once the addition is complete, the solution is allowed to cool without stirring to room temperature. The solid is collected, washed with water (5 x 90 mL), and air-dried to afford 26.7 g of (S)-(+)-BNP acid, $[\alpha]_{546}^{25} +712^\circ$ (methanol, c 0.98) (Note 11). The yield based on enantiomer present in the racemate is 56%. The product is free from contamination by cinchonine, as shown by ^1H NMR, (Me_2SO , 250 MHz) and elemental analysis. HPLC analysis of the methyl ester derivative employing a chiral stationary phase (Note 12) shows the acid to be greater

than 99.4% ee. Partially resolved samples, recovered by adding water to the filtrates, may be purified by crystallization from ethanol or by digestion in hot methanol (Note 13).

(*R*)-(-)-BNP acid. The filtrate from the initial crystallization of the cinchonine salt is evaporated nearly to dryness to give 107 g of crude salt, $[\alpha]_{546}^{25} -113^\circ$ (methanol, d 0.95), consisting of approximately 81% n salt and 19% p salt (Notes 14 and 10). A 2-L, three-necked flask, equipped with addition funnel, reflux condenser, magnetic stirring bar, and thermometer is charged with 107 g of the crude salt and 700 mL of ethanol. The salt is dissolved by heating to reflux, and 790 mL of 6 N hydrochloric acid is added with vigorous stirring over the course of 30 min. The temperature is maintained between 75–80°C during the addition, and the acid begins to precipitate. Once the addition is complete, the solution is allowed to cool without stirring to room temperature. The solid is collected, washed with water (5 x 100 mL), and air-dried to afford 23.3 g of (-)-BNP acid, $[\alpha]_{546}^{25} -717^\circ$ (methanol, d 1.00) (Note 11). The yield based on enantiomer present in the racemate is 49%. The product is free from contamination by cinchonine, as shown by ^1H NMR (Me_2SO , 250 MHz) and elemental analysis. HPLC analysis of the methyl ester derivative employing a chiral stationary phase (Note 12) shows the acid to be 100.0% ee.

2. Notes

1. Commercial dry pyridine, stored over 4 Å molecular sieves, was used without further purification. The 1,1'-bi-2-naphthol is commercially available from Aldrich Chemical Company, Inc. The submitters prepared it by oxidizing a hot aqueous suspension of commercial 98% pure 2-naphthol (Merck-

Schuchardt) with ferric chloride² to obtain crude colored binaphthol (80-90% yield). Unless this material is purified and decolorized by successive crystallization and digestion in hot toluene, the color will be retained in the binaphthylphosphoric acid (60-65% overall yield).

2. The reverse addition of 6 N hydrochloric acid to the pyridine solution results in the formation of a thick and syrupy precipitate, which prevents stirring.

3. Regardless of the conditions of precipitation or crystallization, a polymorphic solvate is obtained which consists of 2 BNP acid:1 pyridine:1 H₂O, according to elemental analyses. Pyridine peaks are apparent in the ¹H NMR spectrum (δ 8.71 and 8.78 in d₆-DMSO). Desolvation occurs at 210-230°C on the Kofler bench or by heating to reflux in 6 N hydrochloric acid.

4. The solubility of BNP acid in water is about 2 g/L at 20°C.

5. The BNP acid is polymorphic. A metastable form, identical with the enantiomers and therefore a conglomerate,³ was sometimes obtained when working above 40°C; the usual stable form is a racemic compound.³ The IR spectrum (Nujol, cm⁻¹) of the racemate is as follows: 950 (strong), 1025 (strong, broad), 1185 (medium), 1200 (strong), 1220 (strong); of conglomerate: 1050 (strong, broad), 1200 (medium), 1230 (strong), 1255 (medium).

6. Commercial (+)-cinchonine (Aldrich Chemical Company, Inc.), [α]_D²⁵ +228° (ethanol, c 0.5), was used without further purification.

7. The checkers observed coloration of this solution and stirred it with 10 g of Norit activated carbon, followed by filtration through a Celite pad. The pad was washed with hot methanol (2 x 50 ml). The submitters did not report any coloration.

8. In order to achieve an efficient resolution it is imperative that the addition of water be even and slow; otherwise premature precipitation or oiling of the cinchonine salt may occur. Likewise, stirring must be maintained during the cooling period to achieve high yields and to avoid the formation of oils. The salt is collected as soon as the mixture cools to room temperature, because the more soluble salt deposits as an oil on standing. The submitters suggest that the yield may be improved by carrying out the crystallization in a cold bath until the solution reaches room temperature. It should be noted that the checkers did not observe crystallization until a packet of seed crystals was opened in their laboratory.

9. The submitters obtained 78.5 g of salt composed of 97% p and 3% n salts, $[\alpha]_{546}^{25} +471^\circ$ (methanol, c 0.9).

10. The p and n salts, prepared from the pure (+)- or (-)-acids and cinchonine and crystallized from methanol-ethyl acetate and methanol-acetone-ethyl acetate, respectively, exhibit the following rotations ($\pm 3\%$) in methanol:

	$[\alpha]_{\lambda}^{25}$				
	589 nm	578 nm	546 nm	436 nm	
p salt	+409°	+428	+492	+890	(c 0.7)
n salt	-211	-222	-256	-474	(c 0.8)

11. Two crystallizations from ethanol did not change the optical rotations of (+)- and (-)-BNP acid, which are as follows:

	$[\alpha]_{\lambda}^{25}$				
	589 nm	578 nm	546 nm	436 nm	365 nm
Methanol	595° ± 7	624 ± 7	720 ± 8	1328 ± 15	2050 ± 25
Ethanol	574 ± 16	602 ± 17	694 ± 20	1267 ± 25	1828 ± 40

Both enantiomers decompose without melting above 300°C. The solid state IR spectra of the enantiomers and the racemate (conglomerate) are identical. The checkers obtained a rotation of -/05° at 546 nm.

12. The methyl ester derivatives were prepared by treating BNP acid with diazomethane in methanol-ether. A Regis Pirkle Type 1-A preparative column (25 cm x 10 mm I.D.) was used and the conditions were as follows: 10% 2-propanol/hexanes, 8.0 mL min⁻¹, detector at 284 nm. The (R)-(-) enantiomer is eluted first and the peaks are well separated (α = 1.24).⁴

13. BNP acid, racemate and enantiomers are sparingly soluble in water and organic solvents, except alcohols. Their solubilities at 25 ± 0.5°C in methanol and 95% ethanol, expressed in g/100 mL of solvent and g/100 mL of solution (in brackets) are given below:

	Racemate	Enantiomer
Ethanol	10.3 ± 0.5 (11.5)	5.7 ± 0.2 (6.7)
Methanol	2.5 ± 0.1 (3.1)	2.1 ± 0.1 (2.6)

As shown by these data, the racemate is approximately twice as soluble as the enantiomers in ethanol, whereas in methanol, the solubilities are nearly the

same. This is because the racemate forms a crystalline compound (solvate) with methanol as shown by IR and NMR (Me_2SO) spectra, and by elemental analysis. The racemate dissolves more rapidly in refluxing methanol than do the enantiomers. Accordingly, partially resolved samples having 80-90% ee can be conveniently purified by merely digesting them for 10-15 min in refluxing methanol. In general, partially resolved BNP acid can be purified by crystallization from ethanol. In this case, the dissolution rate is particularly slow and the desired solution is obtained by using solvent in excess, then concentrating the solution.

14. The submitters obtained 103 g of material consisting of about 85% n and 15% p salts, $[\alpha]_{546}^{25} -150^\circ$ (methanol, c 0.8).

3. Discussion

Marschalk⁵ first prepared BNP acid by the action of phosphorus oxychloride on binaphthol without any solvent, followed by hydrolysis of the isolated acid chloride. The procedure herein described was only briefly mentioned, without any experimental details, in a paper describing the resolution of BNP acid and its use as a resolving agent.^{6a}

The BNP acid has also been prepared by Cram and co-workers⁷ from binaphthol and phosphorus oxychloride, although under quite different conditions, which involved isolation of the intermediate acid chloride, its hydrolysis by aqueous tetrahydrofuran, and extraction of BNP acid with ethyl acetate. In our hands, this extraction could not be carried out without using larger volumes of solvent and water than those reported. More recently, it has also been prepared by Japanese authors who used a slightly modified method.⁸

The resolution of BNP acid by crystallizing the (+)-acid-cinchonine salt, then the (-)-acid-cinchonidine salt, was first mentioned in a short paper and subsequently described in a patent.^{6a}

A modification of this procedure was used by Cram, et al.⁷ who likewise obtained the (+)-BNP acid via its cinchonine salt, but they isolated the (-) enantiomer directly from the more soluble salt, without using cinchonidine, in 59% and 46% respective yields. Both enantiomers, precipitated by 6 N hydrochloric acid from their cinchonine salt solutions, had to be purified by successive digestions with hot 6 N hydrochloric acid and water in order to decompose any remaining cinchonine salt. These purifications are avoided by using the procedure described herein.

BNP acid has also been resolved via its strychnine salt.^{6b}

Some physical properties of BNP acid have been studied (triplet state circular dichroism,^{9a} luminescence, photoracemization.^{9b}).

Derivatives have been prepared: methyl esters (enantiomers and racemate)⁶ and D-glucopyranosyl ester.¹⁰

Enantiomeric (S)-(+)- and (R)-(-)-BNP acids are useful resolving agents, which give well crystallized, easily separated salts with a variety of amines. They have been used in the preparation of the enantiomers of biologically- and therapeutically-active compounds, such as α -difluoromethyl- α -aminovaleric acid,¹¹ cephalosporin,¹² dibenzothiepin,¹³ benzodiazepine derivatives¹⁴ and 3-hydroxyphenyl-N-propylpiperidine.¹⁵ BNP acid also has been used for the direct resolution of underivatized o-tyrosine.¹⁶

(+)-BNP acid, linked to silica gel, has been used in high performance liquid chromatographic resolution of helicenenes.¹⁷

Reduction of (S)-(+)- and (R)-(-)-BNP methyl esters^{6a} or acids⁷ by lithium aluminum hydride, or by Red-Al (this volume, p. 13) yields (S)-(-)- and (R)-(+)-binaphthol, respectively. This is, at present, the most convenient access to optically active binaphthols, used by Cram and co-workers¹⁸ to prepare macrocyclic polyethers and by Japanese authors⁸ in asymmetric synthesis of cyclic binaphthyl-esters.

Racemic and optically active BNP acids (as well as binaphthols) are also available commercially from Aldrich Chemical Company, Inc.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

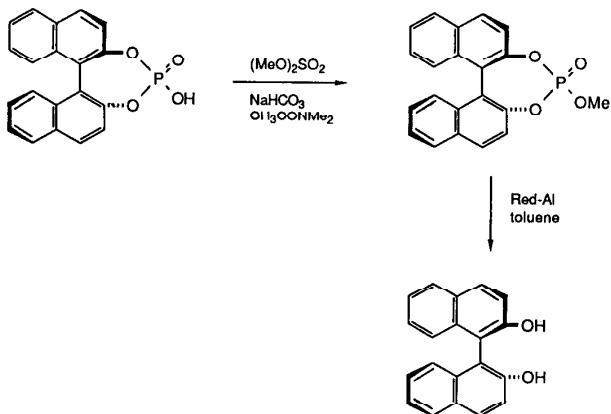
Cinchonine (8); 9S-Cinchonan-9-ol (9); (118-10-5)

Cinchonidine (8); 8 α ,9R-Cinchonan-9-ol (9); (485-71-2)

S(+) BNP acid; S(+) Dinaphtho[2,1-d:1'2'-f][1,3,2]dioxaphosphepin,
4-hydroxy-4-oxide (9); (35193-64-7). Compound with 9S-cinchonan-9-ol
(9); (39749-50-3)

R(-) BNP acid; R(-) Dinaphtho[2,1-d:1'2'-r][1,3,2]dioxaphosphepin,
4-hydroxy-4-oxide (9); (39648-67-4). Compound with 8 α ,9R-cinchonan-9-ol
(9); (40481-36-5)

(R)-(+)-1,1'-BINAPHTHALENE-2,2'-DIOL
 ([1,1'-Binaphthalene]-2,2'-diol, (R)-)



Submitted by Larry K. Truesdale.¹

Checked by Georg W. Schröder and K. Barry Sharpless.

1. Procedure

A. (R)-(-)-Methyl 1,1'-binaphthyl-2,2'-diylphosphate. A 200-mL, three-necked flask equipped with a magnetic stirrer and a gas bubbler is charged with 20.0 g (57.4 mmol) of (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (Note 1), 40 mL of N,N-dimethylacetamide, and 10.0 mL (105.7 mmol) of dimethyl sulfate (Note 2). The resulting pale yellow oil is then treated cautiously in small portions with 10.4 g (123.8 mmol) of sodium bicarbonate.

The addition causes gas evolution and foaming. Foaming subsides after ca. 20 min, and the resulting turbid yellow solution is stirred overnight at room temperature (Note 3).

The reaction mixture is poured into a mixture of 300 mL of toluene and 100 mL of ethyl acetate. The resulting milky solution is washed twice with 100-mL portions of deionized water, twice with 100-mL portions of brine, and then dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator under reduced pressure in a 50°C bath. The semi-solid residue is slurried in 55 mL of ether and then collected by filtration on a sintered glass funnel. After the solid is washed four times with 10 mL ether, it is set aside and the filtrate is evaporated to dryness. The residue is slurried in 10 mL of ether. The solid is collected on a glass frit and washed twice with 10 mL of ether. Both solids are combined and dried under reduced pressure to give 16.4 g (45.2 mmol) (79%) of phosphate as an off-white powder, mp 215-217°C; $[\alpha]_D^{25}$ -526.8° (THF, c 1.16) (Note 4).

B. Crude (R)-(+)-1,1'-binaphthalene-2,2'-diol. [Gases evolved in this step create a stench and are toxic. The use of an efficient fume hood is imperative (Note 5).]

A 2-L, three-necked flask equipped with a Y-tube, magnetic stirrer, dropping funnel topped with a gas bubbler, thermometer, and drying tube is charged with 14.7 g (40.6 mmol) of crude (R)-(-)-methyl 1,1'-binaphthyl-2,2'-diyl phosphate and 350 mL of dry toluene. The mixture is stirred under nitrogen and heated with a steam bath until dissolution occurs (44°C). The solution is then cooled in an ice-water bath to 10°C. The cooling bath is removed and a solution of 27.0 mL (91.8 mmol) of Red-A1 (Note 6) in 35 mL of toluene is added from the dropping funnel over a 90-min period. The mixture

turns yellow, evolves a gas, and heats up to 26°C. Gas evolution ceases 20 min after the addition is completed. TLC analysis (silica gel plate developed with ethyl acetate) indicates that the reaction is complete.

The entire reaction mixture is poured into 430 mL of 10% hydrochloric acid (mild exothermic reaction). The organic layer is separated and washed with another 430-mL portion of 10% hydrochloric acid. After further washes with 150 mL of brine and 160 mL of deionized water, all aqueous layers are combined and back-extracted with a 550-mL portion of 3:2 toluene:methanol and two 300-mL portions of toluene. The combined organic layers are dried over anhydrous sodium sulfate, and filtered. The solvent is removed on a rotary evaporator under reduced pressure in a 45°C bath to give 11.4 g (98%) of crude product as a bright yellow microcrystalline solid, mp 203-205°C.

C. Recrystallization of (R)-(+)-1,1'-binaphthalene-2,2'-diol. A 200-mL flask with a reflux condenser is charged with 11.4 g of crude (R)-(+)-1,1'-binaphthalene-2,2'-diol and 1.5 g of Norit A, and refluxed for 5 min. The hot solution is filtered through a pad of 5 g of Celite on a glass frit. The Celite and Norit A from the frit are slurried together with 1.5 g of Norit A in 70 mL of toluene, refluxed for 5 min, and filtered hot through a pad of 5 g of Celite on a glass frit. The Celite is washed with 70 mL of hot toluene. The combined filtrates are warmed to 50°C to dissolve the precipitated crystals and filtered once again while warm through a pad of 5 g of Celite on a glass frit, which is then washed with 40 mL of hot toluene. The filtrate is freed from solvent on a rotary evaporator and the residue is recrystallized from 75 mL of toluene with stirring. The mixture is stirred overnight at ambient temperature. The resulting suspension is filtered and the filter cake is washed with two 10-mL portions of toluene. The recrystallized product is then dried under reduced pressure (high vacuum) to give 9.62 g of white,

microcrystalline material in the first crop. This material melts at 207-209°C, $[\alpha]_D^{25} +33.6^\circ$ (THF, c 1.11) (Notes 7 and 8).

Concentration of the filtrate and toluene washings under reduced pressure to ca. 11 mL affords, after cooling, collecting, washing three times with 3 mL of toluene, and drying the solid material, a second crop of product which weighs 1.04 g. This crop is an off-white microcrystalline powder, mp 204-206°C and $[\alpha]_D^{25} +33.6^\circ$ (THF, c 1.12) (Note 9).

The two crops (10.66 g) represent 94% recovery on recrystallization. The yield of recrystallized product is 92% in the reductive cleavage of the phosphate ester and 73% overall.

2. Notes

1. The starting material was prepared by the method described in the companion procedure of Fouquey and Jacques (*Org. Synth.* 1988, 67, 1) and had $[\alpha]_D^{25} -704.7$ (MeOH, c 1.0).

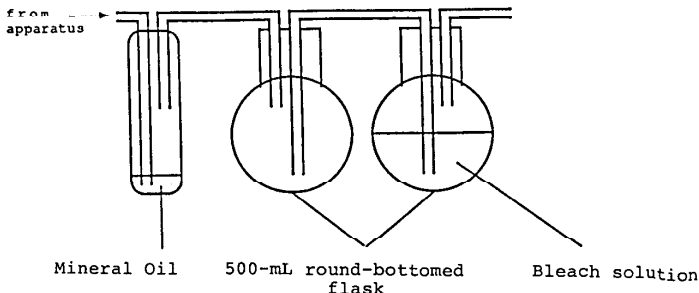
2. Dimethyl sulfate was obtained from Aldrich Chemical Company, Inc. It is highly toxic and carcinogenic, and it should be handled only in a well-ventilated hood.

3. The reaction was complete by TLC (silica-gel plate) analysis. The consumption of starting material and the formation of product can be monitored using a 5:2 (v:v) mixture of ethyl acetate:hexane as the solvent.

4. The enantiomeric excess of this product was determined to be >99.5% using a chiral stationary phase HPLC (preparative Regis Pirkle Type 1-A, 10 x 250 mm I.D., 7.5 mL/min flow rate, 1000 psi pressure, 10% 2-propanol in hexane, detector at 284 nm). The R-(-)-enantiomer is eluted first and the peaks are well separated.² Another batch of phosphate ($[\alpha]_D^{25} -507.7^\circ$, THF, c 1.17) was shown to have 96.5% ee using the same conditions.

The same reaction was also checked on a slightly smaller scale, using 18.8 g (54.0 mmol) of (R)-(-)-1,1'-binaphthyl-2,2'-diyl phosphate. The yield was 81%. The submitters report a yield of 80% for the reaction run on a 1.6 mole scale.

5. The phosphorus hydride which evolves is highly toxic and creates a stench. Therefore the checkers recommend that this reaction as well as the workup be performed in an efficient fume hood. The checkers found it advantageous to scrub the phosphorus hydride which formed in a trap (shown below) by bubbling the evolving gases through a solution of 250 mL of bleach (5% sodium hypochlorite in water). During the reaction a constant flow of nitrogen was applied to avoid contamination of the reaction flask with wet gases from the traps.



6. Red-Al is the Aldrich Chemical Company, Inc., brand of sodium bis(2-methoxyethoxy)aluminum hydride in 3.4 M toluene solution.

7. The enantiomeric excess of this product was determined to be >99.5% using the same conditions as mentioned in Note 4. The peaks are well separated and the R-(+)-enantiomer is eluted second.² Another batch obtained from reduction of phosphate having 96.5% ee had a mp of 207-209°C and $[\alpha]_D^{25}$

+33.5° (THF, c 1.12). This material had an enantiomeric excess of >99.5%, determined under the same conditions as described in Note 4. The submitters report $[\alpha]_D^{25}$ +34.7° (THF, c 1.035) for material with mp 207-209°C [lit.⁵ mp 206.5-207.5°C, $[\alpha]_D^{25}$ +34.3° (THF, c 1.1)].

8. The product has the following spectral properties: ¹H NMR (1:1 CDCl₃:DMSO-*d*₆) δ : 7.04 (d, 2 H, J = 8.8), 7.20-7.35 (m, 4 H), 7.40 (d, 2 H, J = 8.8), 7.92 (d, 2 H, J = 8.8), 9.21 (s, 2 H).

9. The enantiomeric excess of this product was determined to be >99.5% using the same conditions as mentioned in Note 4. Another batch obtained from the reduction of phosphate having 96.5% ee had a mp of 200-204°C and $[\alpha]_D^{25}$ +30.7° (THF, c 1.13). This (second crop) material had an enantiomeric excess of 86.5%, determined under the same conditions as described in Note 4. The submitters report $[\alpha]_D^{25}$ +33.5° (THF, c 0.775) for material with mp 204-206°C.

3. Discussion

Enantiomerically pure 1,1'-binaphthalene-2,2'-diols are used in various types of asymmetric syntheses, for example, as chiral auxiliaries in a method for the asymmetric reduction of ketones.²

The previously published method^{4,5} for the liberation of the diol from the resolved 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate entailed esterification with diazomethane and reductive cleavage with lithium aluminum hydride. The procedure presented here is felt to be safer in that it circumvents the hazards associated with using diazomethane and lithium aluminum hydride on a large scale.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

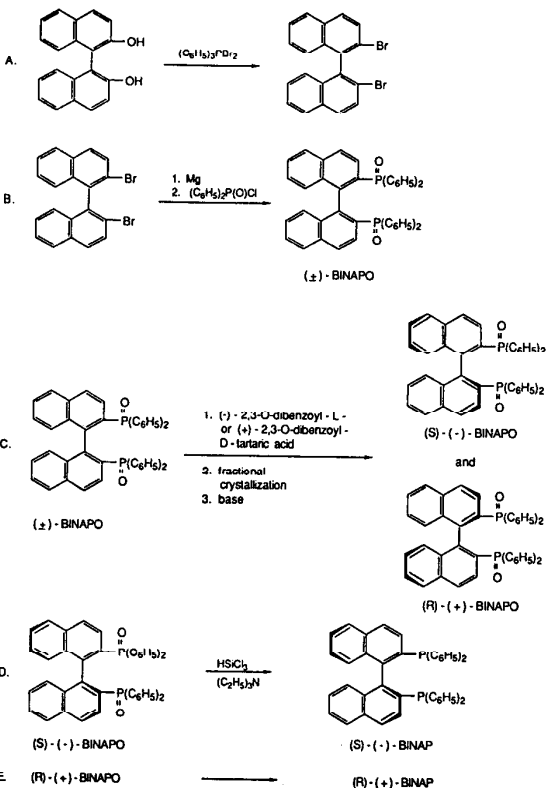
(Registry Number)

(±)-Binaphthol; [1,1'-Binaphthalene]-2,2'-diol (8,9); (41024-90-2), (602-09-5)
 R-(+)-Binaphthol; [1,1'-Binaphthalene]-2,2'-diol (8,9); (18531-94-7)
 S-(-)-Binaphthol; [1,1'-Binaphthalene]-2,2'-diol (8,9); (18531-99-2)
 (R)-(-)-Methyl 1,1'-binaphthyl-2,2'-diyl phosphate: Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphopin, 4-methoxy-, 4-oxide, (R)- (11); (86334-02-3)
 (R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogen phosphate: Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphopin, 4-hydroxy-, 4-oxide, (R)- (9); (39648-67-4)
 Sodium bis(2-methoxyethoxy)aluminum hydride: Aluminate (1-), dihydrobis(2-methoxyethanolato)-, sodium (8); Aluminate(1-), dihydrobis(2-methoxyethanolato-0,0')-, sodium (9); (22722-98-1)

(R)-(+)- AND (S)-(-)-2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-

BINAPHTHYL (BINAP)

(Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl]-, (R)- or (S)-)



Submitted by Hidemasa Takaya^{1a}, Susumu Akutagawa,^{1b} and Ryoji Noyori.^{1c}

Checked by Marco Cereghetti, Alain Raguec, Max Vecchi, and Gabriel Saucy.

1. Procedure

Caution! These operations, which involve toxic reagents, should be conducted in an efficient hood.

A. *2,2'-Dibromo-1,1'-binaphthyl*. A 2-L, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and a dropping funnel. The flask is charged with 240 g (0.915 mol) of triphenylphosphine and 500 mL of dry acetonitrile (Note 1). Stirring is begun and the solid is dissolved by warming the flask with hot water. The solution is then cooled with an ice/water mixture and to this is added dropwise with stirring 155 g (50 mL, 0.969 mol) of bromine over a period of 1 hr. The ice/water bath is removed and 120 g (0.420 mol) of 2,2'-dihydroxy-1,1'-binaphthyl is added to the solution (Note 2). The viscous slurry is stirred at 60°C for 30 min. The flask is now fitted for a simple distillation and most of the solvent is removed by applying partial vacuum. The last trace of acetonitrile is removed at aspirator vacuum using a bath temperature of 100°C. The temperature of the resulting mass is raised carefully by means of a heating mantle (Note 3) to 240-260°C over a period of 1 hr, at which temperature an exothermic reaction occurs (Note 4), with evolution of hydrogen bromide. After the exothermic reaction subsides, the reaction mixture is further stirred at 260-270°C for 1 hr, and then the temperature is gradually raised and kept at 310-320°C for 30 min to complete the reaction. The reaction mixture, a homogenous melt, is allowed to cool to ca. 200°C with stirring and to this is added 1000 mL of Celite with stirring (Note 5). After the mixture is cooled below 70°C, it is extracted with 500 mL of a boiling 1:1 mixture of benzene and hexane. The solid material, separated by filtration through a sintered-glass funnel, is extracted further with three 200-mL

portions of a boiling 1:1 mixture of benzene and hexane. The combined extracts are evaporated to give an orange-yellow viscous oil, which is dissolved in 200 mL of ethanol. The solution is left in a refrigerator for 2 days (Note 6). 2,2'-Dibromo-1,1'-binaphthyl precipitates and is collected on a sintered-glass funnel to give 90 g of the crude product. Recrystallization from ethanol affords the pure dibromide (78.0 g, 45% yield) as pale yellow, fine crystals (Note 7).

B. (\pm)-2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl [(\pm)-BINAPO]. A 1-L, three-necked, round-bottomed flask is provided with a mechanical stirrer, addition funnel, thermometer, and a reflux condenser, the top of which is connected with a bubbler and an argon line by way of a three-way stopcock. The flask is flushed with argon and charged with 2.84 g (0.117 g-atom) of magnesium turnings, 50 mL of dry, degassed tetrahydrofuran (Note 8), 50 mg of iodine, and 0.5 mL of 1,2-dibromoethane. The mixture is stirred at room temperature until the color of iodine fades and evolution of ethylene ceases. The flask is placed in an oil bath, the reaction mixture is stirred and heated at 50°-70°C, and 20.0 g (50.0 mmol) of 2,2'-dibromo-1,1'-binaphthyl in 400 mL of dry, degassed toluene (Note 9) is added over a period of 3.5 hr. The mixture is stirred at 75°C for 2 hr and then cooled to 10°C. To this is added dropwise over a 20 min period a solution of 28.4 g (120 mmol) of diphenylphosphinyl chloride (Note 10) in 35 mL of toluene (Note 9) while the temperature is held at 10-15°C. After the addition is completed, the mixture is further stirred at 60°C for 2 hr, and then cooled to 15°C. To the solution is added dropwise 350 mL of 10% aqueous ammonium chloride and the mixture is stirred for another 10 min at 60°C. The organic layer is separated, washed successively with 150 mL of 10% aqueous ammonium chloride, two 150-mL portions of 1 N sodium hydroxide, and finally with two 150-mL portions of water. The

toluene layer is dried for a short time over anhydrous sodium sulfate (Note 11), filtered, and concentrated under reduced pressure to give 38.8 g of a pale yellow solid. This crude product is stirred with 150 mL of boiling toluene for a few minutes and to this is added 100 mL of heptane. The mixture is allowed to stand at room temperature overnight. The solid product is separated by filtration through a sintered-glass funnel and dried at 70°C (0.05 mm) for 2 hr to give 24.5 g (75%) of (\pm)-BINAPO as a slightly pale yellow solid (Note 12). Concentration of the filtrate and recrystallization of the residue twice from 30-mL portions of toluene gives an additional 3.6 g (11%) of (\pm)-BINAPO. This product is suitable for use in Part C without further purification.

C. *Optical resolution of (\pm)-BINAPO.* A 2-L, round-bottomed flask is equipped with a magnetic stirrer bar and a reflux condenser. The flask is charged with 10.5 g (16.0 mmol) of racemic BINAPO and 700 mL of chloroform (Note 13). The solid is dissolved by heating at reflux temperature with stirring, followed by rapid addition of a warm solution of 6.0 g (16.0 mmol) of (-)-2,3-O-dibenzoyl-L-tartaric acid monohydrate [(-)-DBT monohydrate] (Note 14) in 460 mL of ethyl acetate (Note 13). The mixture is stirred under reflux for 2-3 min and then allowed to stand at room temperature overnight. The crystals formed are collected on a sintered-glass funnel and the filtrate is stored for recovery of (R)-(+)-BINAPO (see below). The solid product is dried at room temperature (0.05 mm) for 6 hr to give 7.2 g (89% of theory) of a 1:1 complex of (S)-BINAPO and (-)-DBT, mp 238-240°C (dec), $[\alpha]_D^{25}$ -170° (ethanol, c 0.503) (Note 15).

This complex (7.1 g, 7.0 mmol) is treated with 150 mL of 0.75 N aqueous sodium hydroxide and the mixture is extracted with two 150-mL portions of chloroform. The combined organic layers are washed with 100 mL of 0.75 N

sodium hydroxide, water, and dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the solvent is evaporated. The residue is washed with 20 mL of cold ethyl acetate to furnish 5.3 g of white solid, which is dried at 80°C (0.05 mm) overnight to give 4.6 g (100% based on the complex used) of (S)-BINAPO, mp 256-258°C, $[\alpha]_D^{25} -392^\circ$ (benzene, c 0.530) (Note 16).

The mother liquor and the filtrate from the first resolution (see above) are combined and concentrated to dryness to give 9.0 g of solid material ((R)-BINAPO and (-)-DBT) after being dried at 80°C (0.05 mm) for 3 hr, mp 228-230°C (dec). This solid is treated with 150 mL of 0.75 N aqueous sodium hydroxide and extracted with two 150-mL portions of chloroform. The combined extract is washed with 70 mL of 0.75 N sodium hydroxide, two 100-mL portions of water, and dried over sodium sulfate. The drying agent is removed by filtration and the filtrate is evaporated to give 7.7 g of colorless solid, which is dried at 80°C overnight to afford 5.9 g (9.0 mmol) of crude (R)-BINAPO, mp 249-251°C, $[\alpha]_D^{20} +304^\circ$ (benzene, c 0.522). This recovered (R)-BINAPO is dissolved in 350 mL of refluxing chloroform and to this is added with stirring a solution of 3.4 g (9.0 mmol) of (+)-DBT monohydrate in 280 mL of warm ethyl acetate. The mixture is stirred at reflux temperature for 5 min and then allowed to stand at room temperature overnight. The white precipitates are collected on a sintered-glass funnel, washed with two 20-mL portions of cold ethyl acetate, and dried at 70°C (0.05 mm) for 12 hr to give 7.5 g [92% yield based on the initially used (R)-BINAPO] of the (R)-BINAPO-(+)-DBT-complex, mp 235-236°C (dec), $[\alpha]_D^{25} +172^\circ$ (ethanol, c 0.527).

This complex (7.3 g, 7.2 mmol) is treated with 200 mL of 0.75 N aqueous sodium hydroxide and extracted twice with 150-mL portions of chloroform. The combined chloroform layer is washed with 60 mL of 0.75 N aqueous sodium hydroxide, two 100-mL portions of water, and dried over anhydrous sodium

sulfate, and filtered. Evaporation of the filtrate affords 5.25 g of colorless solid which is dried at 80°C (0.05 mm) to give 4.65 g (99% yield based on the complex used) of (R)-BINAPO, mp 256-258°C, $[\alpha]_D^{25} +388^\circ$ (benzene, c 0.514) (Note 17).

D. Reduction of (S)-(-)-BINAPO to (S)-(-)-BINAP. In a 300-mL, three-necked flask, fitted with a magnetic stirrer bar, thermometer, and a reflux condenser which is connected through a three-way stopcock to an argon inlet tube and a bubbler, is placed 4.5 g (6.9 mmol) of (S)-BINAPO. The flask is flushed with argon followed by the addition of 100 mL of dry, degassed xylene (Note 9), 4.2 mL of triethylamine (3.1 g, 30 mmol) (Note 9), and 3.0 mL (4.0 g, 29 mmol) of trichlorosilane (Note 13) by means of syringes. The mixture is stirred and heated at 100°C for 1 hr, at 120°C for 1 hr, and finally at refluxing temperature for 6 hr (Note 18). After the solution is cooled to room temperature, 70 mL of 30% aqueous sodium hydroxide solution is carefully added. The mixture is then stirred at 60°C until the organic and aqueous layers become clear, and it is transferred into a 300-mL separatory funnel. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of warm toluene. The combined organic layer is washed with 70 mL of 30% sodium hydroxide solution and three 100-mL portions of water, and then dried over anhydrous sodium sulfate. The organic layer is concentrated under reduced pressure to a volume of about 15 mL and to this is added 15 mL of degassed methanol. The precipitates are collected on a sintered-glass funnel, washed with 15 mL of methanol, and dried at 80°C (0.05 mm) for 6 hr to give 4.2 g (97% yield) of (S)-BINAP as colorless solid, mp 236-238°C, $[\alpha]_D^{25} -223^\circ$ (benzene, c 0.502) (Notes 19 and 20).

2. Notes

1. Reagent grade acetonitrile was dried over 3\AA molecular sieves and then heated at reflux for several hours over calcium hydride and distilled under dry argon.

2. Commercial reagent grade 2,2'-dihydroxy-1,1'-binaphthyl from Aldrich Chemical Company, Inc. (1,1'-bi-2-naphthol) was used as obtained. It also can be prepared by the oxidative coupling of β -naphthol with ferric chloride² and used after recrystallization from ethanol and then benzene.

3. In order to obtain a homogeneous melt, the checkers had to raise the bath temperature to 300-335°C. They preferred a Woods metal bath.

4. Temperature should be carefully controlled. Too rapid heating can result in an uncontrollably vigorous reaction.

5. This facilitates the smooth extraction of the products.

6. This procedure removes triphenylphosphine oxide.

7. The product melts at 184-185°C (lit.³ mp 180°C), R_f 0.50 (E. Merck Kieselgel 60 PF₂₅₄, 1:4 benzene-hexane).

8. Reagent grade tetrahydrofuran was distilled from sodium benzophenone ketyl under argon before use.

9. Commercial guaranteed grade solvents were distilled over finely powdered calcium hydride under argon before use.

10. Commercial reagent grade diphenylphosphinyl chloride from Aldrich Chemical Company, Inc. was used as obtained. This compound can be prepared either by oxidation of diphenylphosphinous chloride with dimethyl sulfoxide⁴ or by the treatment of diphenylphosphinic acid with phosphorus pentachloride.⁵

11. Prolonged standing of the solution at room temperature may cause precipitation of (\pm)-BINAPO. In such a case, warm chloroform can be used to dissolve the solid.

12. The checkers obtained first crops ranging from 76 to 84%, mp 295.5-297°C. The submitters report mp 299-300°C. An analytically pure sample was obtained by recrystallization from a mixture of hexane and toluene, mp 304-306°C. One gram of (\pm)-BINAPO dissolves in 28 mL of boiling toluene.

13. Commercial reagent grade chemicals were used.

14. Guaranteed grade (-)-2,3-O-dibenzoyl-L-tartaric acid monohydrate and its enantiomer were purchased from Tokyo Kasei Kogyo Co., Ltd., and used without further purification.

15. The checkers had yields ranging from 69 to 90%. They determined the enantiomeric purity of the S-BINAPO component, $[\alpha]_D^{20} -168^\circ$ (ethanol, c 0.5), to be 99.6/0.4 using a Pirkle column (Note 16). The submitters report that recrystallization from a 1:2 mixture of ethyl acetate and chloroform gave an analytically pure sample, mp 240-241°C (dec), $[\alpha]_D^{24} -174^\circ$ (ethanol, c 0.523).

16. The checkers obtained first crops of 87% and 75.8%, mp 263-263.5°C, $[\alpha]_D^{20} -389^\circ$ (benzene, c 0.5), and mother liquors of 11% and 13.5% respectively. These materials were analyzed on a Pirkle column (Baker bond II) with hexane/ethanol mixtures and found to have S/R ratios of 99.7/0.3 (first crop) and 93/1.7 (mother liquor). The submitters report obtaining analytically pure (S)-BINAPO by recrystallization from a mixture of hexane and toluene, mp 261-262°C, $[\alpha]_D^{24} -396^\circ$ (benzene, c 0.467).

17. The submitters obtained analytically pure (R)-BINAPO by recrystallization from a mixture of hexane and toluene, mp 262-263°C, $[\alpha]_D^{24} +399^\circ$ (benzene, c 0.500). See Note 16 for determination of optical purity. The checkers found an R/S ratio of 98.8/1.2 for unrecrystallized material, mp 261-261°C, $[\alpha]_D^{20} +379^\circ$ (benzene, c 0.5).

18. During this period a white solid forms at the bottom of the reflux condenser. Use of a ground-glass joint as large as possible is recommended to avoid clogging.

19. GLC analysis (OV-101, capillary column, 5 m, 200-280°C) indicates that the product has a purity of 97%. Trace amounts of BINAPO and the monooxide of BINAP were detected by TLC analysis (E. Merck Kieselgel 60 PF₂₅₄, 1:19 methanol-CHCl₃); R_f 0.42 (BINAPO), 0.67 (monooxide of BINAP), and 0.83 (BINAP). The submitters report that recrystallization from a 1:1 mixture of toluene and ethanol affords optically pure (S)-BINAP, mp 241-242°C, $[\alpha]_D^{25}$ -229° (benzene, c 0.312). The checkers oxidized a sample of first crop material, mp 241-242.5°C, $[\alpha]_D^{20}$ -221° (benzene, c 0.5), for Pirkle analysis (see Note 16). This gave an S/R ratio of 98.2/1.7.

20. The checkers also reduced (R)-(+)-BINAPO to (R)-(+)-BINAP by this procedure. In the best of two runs, first crop material (94.8%), mp 241-242°C, $[\alpha]_D^{20}$ +217° (benzene, c 0.5), with an R/S ratio of 99.0/0.8 was obtained.

3. Discussion

BINAP is a new type of fully aryl-substituted diphosphine with only an axial element of chirality. Optically pure BINAP was first synthesized by the optical resolution of (±)-BINAP using optically active di- μ -chlorobis[(S)-N,N-dimethyl- α -phenylethylamine-2C,N]dipalladium.⁶ The phosphine is also obtained by stereospecific transformation of optically active 2,2'-dibromo-1,1'-binaphthyl.^{6b,7} The procedure outlined here,⁸ however, is the best preparative-scale synthesis of both enantiomers of BINAP in an optically pure state starting from easily accessible racemic 2,2'-dihydroxy-1,1'-binaphthyl. This

method is applicable to various BINAP analogues.⁸ The absolute configuration of (+)-BINAP was determined to be R by X-ray analysis of the complex [Rh((+)-binap)(norbornadiene)]ClO₄.⁹ BINAP serves as an excellent ligand for the Rh(I)-catalyzed asymmetric hydrogenations of α -(acylamino)acrylic acids and esters.⁶ The ligand has also been successfully applied to the Rh(I)-catalyzed asymmetric isomerization of diethylnerylamine or diethylgeranylamine into citronellal (E)-N,N-diethylenamine (this volume, p. 33).¹⁰ This reaction is now used for commercial production of (-)-menthol. In addition, BINAP-based Ru(II) complexes¹¹ catalyze highly enantioselective hydrogenation of alkyl- or aryl-substituted acrylic acids,¹² enamides leading to isoquinoline alkaloids,¹³ allylic and homoallylic alcohols,¹⁴ β -keto esters,¹⁵ other functionalized ketones,¹⁶ etc.

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Appendix

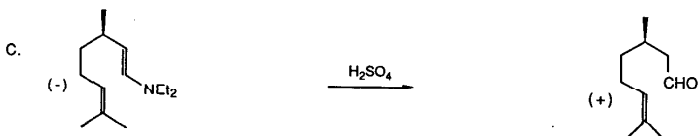
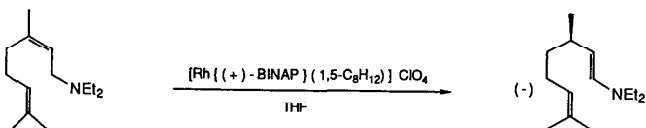
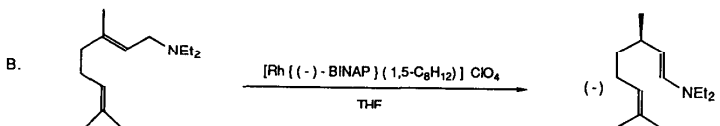
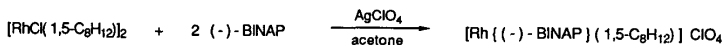
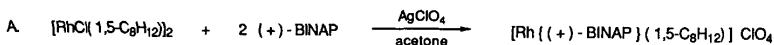
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (R)-(+)- and (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP):
Phosphine, [1,1'-binaphthalene]-2,2'-diylbis-[diphenyl-, (R)- or (S)- (10);
[(R)-: 76189-55-4; (S)-: 76189-56-5]
- 2,2'-Dibromo-1,1'-binaphthyl: 1,1'-Binaphthalene, 2,2'-dibromo- (10);
(74866-28-7)
- 1,1'-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol (8); (602-09-5); [1,1'-
Binaphthalene]-2,2'-diol, (±)- (9); (41024-90-2)
- (±)-2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl [(±)-BINAPO]:
Phosphine oxide. [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-,
(±)- (11); (86632-33-9)
- Diphenylphosphinyl chloride: Phosphinic chloride, diphenyl-
(8,9); (1499-21-4)
- (-)-2,3-O-Dibenzoyl-L-tartaric acid monohydrate [(-)-DBT monohydrate]:
Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]- (9); (2743-38-6)
- (S)-(-)-2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl [(S)-(-)-BINAPO]:
Phosphine oxide, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (S)- (11);
(94041-18-6)
- (+)-2,3-O-Dibenzoyl-D-tartaric acid monohydrate [(+)-DBT monohydrate]:
Tartaric acid, dibenzoate, (-)- (8); Butanedioic acid, 2,3-bis(benzoyloxy)-,
[S-(R*,R*)]- (9); (17026-42-5)

(R)-(+)-2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl [(R)-(+)-BINAP0]:
Phosphine oxide, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (R)- (11);
(94041-16-4)

Trichlorosilane: Silane, trichloro- (8,9); (10025-78-2)

(R)-(-)-N,N-DIETHYL-(E)-CITRONELLAENAMINE AND (R)-(+)-CITRONELLAL
 VIA ISOMERIZATION OF N,N-DIETHYLGERANYLAMINE OR N,N-DIETHYLNERYLAMINE
 (1-(E), 6-Octadienylamine, (R)-(-)-N,N-diethyl-3,7-dimethyl-
 and 6-octenal, (R)-(+)-3,7-dimethyl-)



Submitted by Kazuhide Tani,^{1a} Tsuneaki Yamagata,^{1a} Sei Otsuka,^{1a}

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Checked by David Coffen, Louis A. Portland, Bryant Rossiter,
 and Gabriel Saucy.

1. Procedure

Caution! All manipulations for the preparation of the transition metal complexes and the catalytic isomerisation should be carried out under dry nitrogen or argon. All solvents used are distilled under dry nitrogen over metallic sodium, or after drying over calcium sulfate (in the case of acetone) immediately before use.

A. *[(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]-(η^4 -1,5-cyclo-octadiene)rhodium(I) perchlorate. $[\text{Rh}\{(+)\text{-BINAP}\}(1,5\text{-C}_8\text{H}_{12})]\text{ClO}_4$. A dry, 250-mL Schlenk flask, filled with dry nitrogen or argon and equipped with a magnetic stirring bar, is charged with 0.53 g (1.08 mmol) of chloro-(1,5-cyclooctadiene)rhodium(I) dimer (Note 1). Then 40 mL of dry acetone is added using an air-tight syringe. The flask is protected from light by wrapping it with aluminum foil and 0.45 g (2.17 mmol) of silver perchlorate is added to the stirred suspension. The mixture is stirred for 1 hr at ambient temperature. The colorless precipitate of silver chloride is removed by suction filtration under argon through a stainless steel cannula fitted with a filter tip (Note 2). The precipitates are washed with 5 mL of acetone. To the pale orange filtrate and the washings is added 1.34 g (2.16 mmol) of (+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((+)-BINAP) (Note 3) and the resulting dark red solution is stirred under argon for 18 hr at ambient temperature. The reaction mixture is concentrated under reduced pressure (60 mm) to ca. 3 mL. Then 30 mL of ether is slowly added with a syringe. The resulting mixture is stirred at ambient temperature for 18 hr. The orange solid is filtered off under argon and washed with 5 mL of ether. The crude product is dissolved in 50 mL of dry acetone and the solution is concentrated to ca. 3 mL under 60 mm pressure. Dry ether (30 mL) is slowly added and the*

mixture is stirred for 18 hr. The deep orange crystals are collected by filtration, washed with 5 mL of dry ether, and dried under vacuum to afford 2.07 g of recrystallized product, 230-235°C (dec) (Note 4).

[(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl](η^4 -1,5-cyclooctadiene)-rhodium(I) perchlorate: $[Rh\{(-)-BINAP\}(1,5-C_8H_{12})]ClO_4$ is similarly prepared from 0.53 g (1.09 mmol) of chloro (1,5-cyclooctadiene)rhodium(I) dimer, 0.45 g (2.17 mmol) of silver perchlorate, and 1.34 g (2.16 mol) of (-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((-)-BINAP) (Note 5) in acetone. The crude product is recrystallized from acetone-ether as above to give 2.02 g of orange powder, mp 230°C (dec) (Note 6).

B. *(R)-(-)-N,N-Diethyl-(E)-citronellalenamine [(R)-(-)-N,N-diethyl-3,7-dimethyl-1(E),6-octadienylamine].* From *N,N-diethylgeranylamine*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and an argon inlet is charged with 373 mg (0.40 mmol) of *[(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](η^4 -1,5-cyclooctadiene)rhodium(I) perchlorate*. The flask is evacuated and refilled with argon four times. Another 500-mL, three-necked, round-bottomed flask is charged with 83.8 g (0.40 mol) of *N,N-diethylgeranylamine* (Note 7) and 250 mL of distilled tetrahydrofuran (Note 8) under an argon blanket. This solution is transferred under argon by cannula to the flask containing the catalyst, which is then evacuated and refilled with argon twice. The reaction mixture is stirred and heated at reflux for 21 hr (Note 9). The solution is cooled to room temperature and the solvent is removed under vacuum (60 mm) at 45°C. The residue is vacuum distilled through a 10-cm Vigreux column to give 78.7 g (93.9%) of *(R)-(-)-N,N-diethyl-(E)-citronellalenamine* as a colorless liquid, bp 84-85°C (1.1 mm), $[\alpha]_D^{25} -66.5^\circ$ (hexane, c 10.2). The product is 97.2% chemically pure by GLC analysis (Notes 10, 11 and 12).

From *N,N*-diethylnerylamine. Similarly, 83.8 g (0.40 mol) of *N,N*-diethylnerylamine (Note 13) is isomerized with 373 mg (0.40 mmol) of [(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](η⁴-1,5-cyclooctadiene)rhodium(I) perchlorate catalyst in 250 mL of THF (Note 8) at reflux for 70 hr (Note 9) to give 77.2 g (92.1%) of (R)-(-)-*N,N*-diethyl-(E)-citronellaleneamine, $[\alpha]_D^{25} -66.9^\circ$ (hexane, *c* 10.7). The chemical purity of the product is 91.7% by GLC (Notes 10, 12, and 14).

C. (R)-(+)-Citronellal. [(R)-(+)-3,7-Dimethyl-6-octanal]. A 500-mL, round-bottomed flask equipped with a magnetic stirrer and an ice bath is charged with 33.4 g (0.16 mol) of (R)-(-)-*N,N*-diethyl-(E)-citronellaleneamine in 80 mL of ether at 0°C. To this stirred solution is added 80 mL of a 1:4 glacial acetic acid-deionized water solution in one portion (Note 15). The reaction mixture is stirred for 5 min at 0°C and then at room temperature for 25 min. The ether layer is separated and washed successively with 50 mL of water, two 50-mL portions of saturated aqueous sodium bicarbonate solution, 50 mL of water, and 50 mL of saturated brine. The ether layer is dried over anhydrous sodium sulfate and filtered (Note 16). The ether solution is concentrated at 40°C under reduced pressure (60 mm) to a pale yellow liquid. The liquid is distilled through a 10-cm Vigreux column to give 22.5 g (91.4%) of (+)-citronellal as a colorless liquid, bp 79-80°C (7 mm), $[\alpha]_D^{25} +15.7^\circ$ (neat, *d* 0.851). The product is 99.4% chemically pure by GLC and has an optical purity of 95.2% (Note 17).

2. Notes

1. Chloro(η^4 -1,5-cyclooctadiene)rhodium(I) dimer, $[\text{RhCl}(1,5\text{-C}_8\text{H}_{12})]$ can be prepared according to the method described in *Inorganic Syntheses*.² The checkers used material purchased from the Aldrich Chemical Company, Inc.

2. This can also be done as previously described in *Inorganic Syntheses*.³

3. (R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl was prepared according to Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1988**, *67*, 20.

4. The submitters obtained 1.5-1.7 g of analytically pure material with mp 164°C (dec). The ^1H NMR (CD_2Cl_2) of this product showed signals at δ : 2.00-2.62 (m, 8 H, $-\text{CH}_2-$), 4.58 (br signal, 2 H, $-\text{CH}=\text{}$), 4.84 (br signal, 2 H, $-\text{CH}=\text{}$), 6.42-8.22 ppm (m, 32 H, arom.); Anal. Calcd for $(\text{C}_{52}\text{H}_{44}\text{ClO}_4\text{Rh})$: C, 66.93; H, 4.75; Cl, 3.80. Found: C, 66.66; H, 4.89; Cl, 3.92.

5. (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl was prepared according to the *Organic Syntheses* procedure; see Note 3.

6. The submitters used THF-ether for recrystallization, in which case the product was obtained as a THF-solvated complex, $[\text{Rh}\{(-)\text{-BINAP}\}(1,5\text{-C}_8\text{H}_{12})]\text{ClO}_4 \cdot \text{THF}$, in the form of deep orange crystals, mp 153°C (dec). It's ^1H NMR (CD_2Cl_2) spectrum showed clearly the presence of the solvating tetrahydrofuran; δ : 1.60-2.00 (m, 4 H, $-\text{CH}_2-$ of THF), 2.00-2.62 (m, 8 H, $-\text{CH}_2-$), 3.40-3.80 (m, 4 H, $-\text{CH}_2\text{O}-$ of THF), 4.58 (br signal, 2 H, $-\text{CH}=\text{}$), 4.82 (br, signal, 2 H, $-\text{CH}=\text{}$), 6.40-7.97 (m, 32 H, arom.); Anal. Calcd for $(\text{C}_{52}\text{H}_{44}\text{ClO}_4\text{RhC}_4\text{H}_8\text{O})$: C, 66.90; H, 5.21; Cl, 3.53. Found: C, 66.55; H, 5.62; Cl, 3.68.

7. N,N-Diethylgeranylamine was prepared according to the method described in *Org. Synth.* 1988, 67, 44. The submitters used material of 99.7% purity (determined by GLC, Hitachi 063 with OV-101 in Fused Silica, 0.2 mm x 25 m column) that was obtained by careful distillation through a column with one hundred theoretical plates, bp 70°C (2 mm), and redistilled over calcium hydride before use. The checkers used a 32-cm Goodloe column and collected the amine at 105°C (2.4 mm), which had a purity of 100% (GLC).

8. Acetone or methanol also may be used. However, tetrahydrofuran gives the best results. The solvents should be strictly dry because water deactivates the catalyst.

9. The submitters ran the reaction at 60°C for 24 hr.

10. Purity of the product and progress of the isomerization can be determined by GLC (Triton X 305 packed in a 0.2 mm x 30 m glass column from Gasukuro Kogyo Co. Ltd., or a column-crosslinked 5% phenylmethyl silicone, 25 m high performance capillary column supplied by Hewlett Packard. Starting temperature, 125°C; rate 3°/min; final temperature, 180°C.) The product enamine is 100% (E)-isomer. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 3045, 2960, 2915, 2860, 2720, 1660, 1655, 1450, 1377, 1298, 1245, 1196, 1100, 985, 937, 886, 830, 784, 740; ^1H NMR (acetone d_6) δ : 0.96 (d, 3 H, $J = 7.2$), 1.01 (t, 6 H, $J = 7.1$), 1.1-1.4 (m, 2 H), 1.58 (br s, 3 H), 1.66 (br s, 3 H), 1.8-2.1 (m, 3 H), 2.92 (q, 4 H, $J = 7.1$), 3.93 (d of d, 1 H, $J = 14.6, 8.4$), 5.11 (br t, 1 H, $J = 7.3$), 5.79 (d of d, 1 H, $J = 14.6, 0.8$).

11. The submitters report 92-96% yields of 98% chemically pure product, bp 80-82°C (1 mm), $[\alpha]_D^{25} -74.3^\circ$ (hexane, c 10.0). The specific rotation was corrected for this purity (Note 12). A specific rotation of $[\alpha]_D^{21} -77.6^\circ$ (hexane) is estimated for the pure enamine.

12. The product is very moisture sensitive and should be handled under dry nitrogen or argon. Despite this precaution, the product is always contaminated by small amounts of (+)-citronellal, which has an optical rotation opposite to that of the enamine. To determine the optical purity of the product enamine, the specific rotation measured therefore must be corrected for the (+)-citronellal impurity. It is more reliable to base optical purity on the specific rotation of the citronellal obtained by hydrolysis of the enamine (Part C). The absolute method using HPLC of the diastereomeric amide derivative⁴ also may be useful as a check of the optical purity.

13. N,N-Diethylnerylamine was prepared according to the method described in *Org. Synth.* 1988, 67, 40, and distilled over calcium hydride and stored under nitrogen below -20°C. GLC-MS analysis (Hitachi 063 and Hitachi RMU-6MG with OV-101 in Fused Silica, 0.2 mm x 25 m column) of N,N-diethylnerylamine used by the submitters showed a purity of 94.9%, and contained N,N-diethyl-2-ethylidene-6-methyl-5-heptenylamine (0.2%), N,N-diethyl-2,7-dimethyl-2,6-octadienylamine (1.5%), N,N-diethyl-3-methylene-7-methyl-6-octenylamine (2.1%), and unidentifiable products (1.3%) as impurities, but not the (E)-isomer, N,N-diethylgeranylamine. The checkers distilled the nerylamine through a 32-cm Goodloe column, bp 102°C (3 mm), and achieved a purity of 98.6%.

14. The submitters obtained 90-95% yields of 94% chemically pure product, $[\alpha]_D^{24}$ -73.1° (hexane, c 10.0; corrected for the citronellal impurity).

15. The submitters conducted the hydrolysis step in a mixture of 2N sulfuric acid and toluene. The acid is added dropwise at 0°C at a rate that keeps the pH of the mixture at 4-5. Control of pH is critical.

16. Rapid work-up after the acid-hydrolysis is desirable.

17. A specific rotation of $[\alpha]_D^{25} +16.5^\circ$ (neat) is reported for optically pure citronellal.⁵

3. Discussion

(R)-(+)-Citronellal is a useful, key intermediate for the preparation of several important, optically active compounds such as citronellol, 1-menthol,⁵ muscone,⁶ and α -tocopherol.⁷ The optical purity of citronellal from natural sources is at most 77% ee, however. This new procedure gives (R)-(+)-citronellal of high optical purity (over 95% ee).

The intermediate enamine, (R)-(-)-N,N-diethyl-(E)-citronellal enamine, is also a key intermediate for preparation of useful, optically-active compounds, e.g., (+)-7-hydroxydihydrocitronellal.⁸

Isomerization of N,N-diethylnerylamine with $[\text{Rh}\{(-)\text{-BINAP}\}(1,5\text{-C}_8\text{H}_{12})]\text{ClO}_4$ and N,N-diethylgeranylamine with $[\text{Rh}\{(+)\text{-BINAP}\}(1,5\text{-C}_8\text{H}_{12})]\text{ClO}_4$ under similar conditions to those described in the text ($[\text{substrate}]/[\text{Rh}] = 100$, in THF, 40°C, 23 hr) proceed equally efficiently to give (+)-N,N-diethyl-(E)-citronellal enamine in good chemical (97% and 95%, respectively) and optical yields (92% and 96%, respectively). Thus, unnatural (S)-(-)-citronellal with high optical purity (over 95% ee) can also be prepared by the new procedure. The substrates must be geometrically pure and the chiral ligand enantiomerically pure in order to achieve optimal results.

If extreme care is taken to purify the substrate and the solvent, the $[\text{substrate}]/[\text{Rh}]$ ratio can be raised much higher. For example, N,N-diethylgeranylamine can be isomerized in tetrahydrofuran in the presence of 0.00125 mol% of $[\text{Rh}\{(-)\text{-BINAP}\}(1,5\text{-C}_8\text{H}_{12})]\text{ClO}_4$ at 100°C in a glass autoclave during 3-7 hr to give (-)-N,N-diethyl-(E)-citronellaleneamine with 97% ee in almost quantitative yield.

With the same catalyst systems, other prochiral N-alkyl- or N,N-dialkylallylamines can also be isomerized efficiently to the corresponding optically active imines or (E)-enamines, respectively. For example, with $[\text{Rh}\{(+)\text{-BINAP}\}(1,5\text{-C}_8\text{H}_{12})]\text{ClO}_4$, ($[\text{substrate}]/[\text{Rh}] = 100$, in THF, 40°C, 23 hr) a secondary allylamine, N-cyclohexylgeranylamine, and an allylamine with styrene-type conjugation, N,N-dimethyl-3-phenyl-2(E)-butenylamine, are isomerized to give (S)-(-)-N-cyclohexylcitronellalimine (chemical yield, 100%; optical yield, 96%) and (R)-(-)-N,N-dimethyl-3-phenyl-1(E)-butenylamine (chemical yield, 84%; optical yield, 90%), respectively.

Under similar conditions, various kinds of N,N-dialkylamines with substituents at β - or γ -positions, e.g., N,N-dimethyl-2-propenylamine, N,N-dimethyl-2(E)-butenylamine, N,N-dimethyl-2-methyl-2-propenylamine, and N,N-dimethyl-3-methyl-2-butenylamine can also be isomerized to the corresponding (E)-enamine in medium to good yields (60, 52, 97, and 100%). However, N,N-dimethyl-2(E)-butenylamine and N-phenyl- or N,N-diphenylgeranylamine were found to be poor substrates.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-(-)-N,N-Diethyl-(E)-citronellal-amine: 1,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, [R-(E)]- (10); (67392-56-7)

(R)-(+)-Citronellal: 6-Octenal, 3,7-dimethyl-, (R)-(+)- (8,9); (2385-77-5)

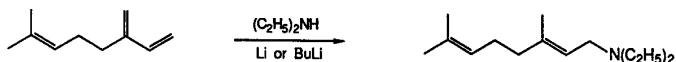
N,N-Diethylgeranylamine: 2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, (E)- (9); (40267-53-6)

N,N-Diethylnerylamine: 2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, (Z)- (9); (40137-00-6)

$[(+)\text{-}2,2'\text{-Bis(diphenylphosphino)-}1,1'\text{-binaphthyl-(}\eta^4\text{-}1,5\text{-cyclooctadiene)rhodium(I) perchlorate: Rhodium(1+), [[1,1'\text{-binaphthalene]-}2,2'\text{-diylbis[diphenylphosphine]-P,P'}][(1,2,5,6\text{-}\eta)\text{-}1,5\text{-cyclooctadiene]-, stereoisomer, perchlorate (11); (82822-45-5)}$
 $\text{Di-}\mu\text{-chlorobis}(\eta^4\text{-}1,5\text{-cyclooctadiene)dirhodium(I): Rhodium, di-}\mu\text{-chlorobis}(1,5\text{-cyclooctadiene)di- (8); Rhodium, di-}\mu\text{-chlorobis}[(1,2,5,6\text{-}\eta)\text{-}1,5\text{-cyclooctadiene}]di- (9); (12092-47-6) \text{ silver perchlorate: Perchloric acid, silver(1+) salt, monohydrate (8,9); (14242-05-8)}$
 $(R)\text{-}(+)\text{- and } (S)\text{-}(-)\text{-}2,2'\text{-Bis(diphenylphosphino)-}1,1'\text{-binaphthyl [BINAP]: Phosphine, [1,1'\text{-binaphthalene]-}2,2'\text{-diylbis[diphenyl-, (R)- or (S)- (10); [(R)-: (76189-55-4); (S)-: (76189-56-5)]}$
 $[(-)\text{-}2,2'\text{-Bis(diphenylphosphino)-}1,1'\text{-binaphthyl}](\eta^4\text{-}1,5\text{-cyclooctadiene)rhodium(I) perchlorate: Rhodium(1+), [[1,1'\text{-binaphthalene]-}2,2'\text{-diylbis[diphenylphosphine]-P,P'}][(1,2,5,6\text{-}\eta)\text{-}1,5\text{-cyclooctadiene]-, stereoisomer, perchlorate (11); (82889-98-3)}$

ADDITION OF DIALKYLAMINES TO MYRCENE: N,N-DIETHYLGERANYLAMINE

(2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-,(E))



Submitted by Kunihiro Takabe,¹ Takashi Katagiri,¹ Juntaro Tanaka,¹
Tutomu Fujita,² Shoji Watanabe,² and Kyoichi Suga.²

Checked by Alan J. Chalk, Laszlo V. Wertheimer, and Gabriel Saucy.

1. Procedure

In a 50-mL, round-bottomed glass reactor equipped with a magnetic stirring bar are placed 13.60 g (74 mmol) of myrcene (Note 1), 10.29 g (141 mmol) of diethylamine (Note 2) and 0.185 g (0.0267 g-atom) of metallic lithium cut into small pieces. The vessel is flushed with dry nitrogen, and is sealed. The solution is heated to 55°C in a water-bath, and is stirred for 5 hr. The vessel is cooled to room temperature and the contents are poured into 30 mL of ice-water. The upper organic layer is separated, and the aqueous layer is extracted with 20-mL portions of diethyl ether. The combined organic layer is washed with aqueous sodium sulfate solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Distillation (Note 3) of the residual liquid affords 1.2-2.0 g of unreacted myrcene and 12.66-13.28 g (74-77%) of the product as a colorless liquid, bp 67-68°C (0.5 mm). GLC analysis indicated that the product contained 91.2-92.5% of N,N-diethylgeranylamine and other isomers (Note 4).

The checkers found that the use of benzene (20 mL) as a solvent increased the selectivity for N,N-diethylgeranylamine to 94% (Notes 5, 6).

A similar reaction of myrcene with dipropylamine (50°C, 20 hr) afforded N,N-dipropylgeranylamine (80%; bp 93-94°C, 1 mm).

2. Notes

1. Myrcene, obtained from SCM Organic Chemicals (also available from Takasago Perfumery Company, Ltd., in Japan), was distilled (bp 69-70°C, 20 mm) prior to use. GLC analysis (Triton X-305, 0.28 mm x 30 m, 80-120°C) showed that the fraction contained 74% myrcene. The submitters used 80% pure myrcene.

2. Diethylamine, obtained from Aldrich Chemical Company, Inc. (also available from Nakarai Chemicals, Ltd., in Japan), was distilled from calcium hydride before use.

3. A short-path distillation apparatus was used in order to prevent loss of the product.

4. GLC analysis (Triton X-305; 0.28 mm x 30 m, 80-160°C) showed a composition of 92% N,N-diethylgeranylamine and other isomers which were identified by the checkers.³ The spectral properties of N,N-diethylgeranylamine are as follows: IR (neat) cm^{-1} : 1660, 1200, 1165, 1050, 830; $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 0.96 (t, 6 H, $J = 7$), 1.44-1.67 (m, 6 H), 1.85-2.15 (m, 4 H), 2.40 (q, 4 H, $J = 7$), 2.92 (d, 2 H, $J = 6.5$), 4.77-5.30 (m, 2 H).

5. The submitters preferred butyllithium in hexane in place of lithium metal, as follows: In a 50-mL, round-bottomed flask equipped with a magnetic stirring bar, are placed 4.08 g (24 mmol) of myrcene and 3.29 g (45 mmol) of diethylamine under nitrogen. The mixture is cooled to 0°C using an ice bath.

and 3.0 mL (4.8 mmol) of a 1.60 M solution of butyllithium in hexane is added dropwise by syringe while stirring for 15 min. The flask is sealed, the solution is warmed to 50°C and stirred for 4 hr. The vessel is cooled to room temperature, and the contents are poured into 20 mL of cold water. The vessel is washed with 30 mL of diethyl ether and 10 mL of water. The upper layer is separated, and the aqueous layer is extracted twice with 20 mL of diethyl ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Distillation (Note 3) of the residual liquid affords a 0.31-0.42 g forerun of unreacted myrcene and 4.06-4.37 g of the product (77-83%) as a colorless liquid, bp 84-86°C (1.5); composition by GLC: 95.3% N,N-diethylgeranylamine and 4.5% other isomers.

6. The submitters report that sodium naphthalenide can be used in place of butyllithium. Using tetrahydrofuran as a solvent, they obtained N,N-diethylgeranylamine in 56% yield.

3. Discussion

N,N-Dialkylgeranylamines have been prepared by the reaction of dialkylamines with geranyl halides.^{4,5} The procedure described here is a modification of one we reported earlier.^{4,6} It is a simple, one-step synthesis of N,N-dialkylgeranylamines from myrcene and dialkylamines which are readily available bulk chemicals. The reaction proceeds stereoselectively, and yields are high.

N,N-Diethylgeranylamine is a key intermediate for the synthesis of industrially important acyclic monoterpenes such as geranyl acetate,⁷ linalool,⁸ citral⁹ and citronellal.¹⁰

1. Department of Synthetic Chemistry, Faculty of Engineering, Shizuoka University, Johoku, Hamamatsu 432, Japan.
2. Department of Applied Chemistry, Faculty of Engineering, Chiba University, Yayoicho, Chiba 280, Japan.
3. Chalk, A. J.; Magennis, S. A. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 286-301.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Myrcene: 1,6-Octadiene, 7-methyl-3-methyleno- (8,9); (123-35-3)
 N,N-Diethylgeranylamine: 2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-,
 (E)- (9); (40267-53-6)

2. Notes

1. The glass autoclave must be used with appropriate precaution. A pressure of about 20 p.s.i. is generated, so a low positive pressure reactor, such as a shielded Fischer-Porter Bottle (Fischer and Porter Company, Lab-Coest Division, Warminster, PA 18974), can be used instead. Alternatively the reaction may be carried out without pressure equipment in 3 days.²

2. Isoprene, obtained from Aldrich Chemical Company, Inc. (also available from Nakarai Chemicals, Ltd. in Japan), was dried over Linde-type 4A molecular sieves for at least 1 day and freshly distilled prior to use.

3. Diethylamine, obtained from Aldrich Chemical Company, Inc., was distilled from calcium hydride before use.

4. A slow stream of dry nitrogen was passed through an inverted funnel that was placed over the vessel.

5. Butyllithium in hexane was obtained from Aldrich Chemical Company, Inc. (also available from Nakarai Chemicals, Ltd. in Japan), and titrated before use.³ Lithium (0.055 g, 0.0079 g-atom), cut into small pieces (ca. 2 mm), can be used in place of the butyllithium-hexane solution.

6. A forerun (1.4-0.6 g) boiling at 52-56°C (16 mm) consists mainly of N,N-diethyl-2-methyl-2-butenylamine and N,N-diethyl-3-methyl-2-butenylamine.

7. GLC analysis (7% Apiezon L on 60-80 mesh Gaschrom Q, 3 mm x 3 m, 170°C) showed that the product is over 99% isomerically pure. The spectral properties of N,N-diethylnerylamine are as follows: IR (neat) cm^{-1} : 1660, 1200, 1165, 1050, 830; ^1H NMR (CDCl_3) δ : 1.03 (t, 6 H, $J = 7$, CH_3 -), 1.45-1.7 (m, 6 H, $\text{CH}_3\text{-C=}$), 2.02-2.2 (m, 4 H, $\text{-CH}_2\text{-C=}$), 2.50 (q, 4 H, $J = 7$, $\text{-N-CH}_2\text{-}$), 3.05 (d, 2 H, $J = 6.5$, $\text{-N-CH}_2\text{-C=}$), 4.9-5.5 (m, 2 H, -CH=).

8. The submitters report that similar reactions of isoprene with dimethylamine (55°C, 10 hr) and dipropylamine (65°C, 15 hr) afforded N,N-dimethylnerylamine (69%), bp 85-86°C (9 mm) and N,N-dipropylnerylamine (77%), bp 86-87°C (1 mm), respectively.

3. Discussion

The procedure described here is essentially that reported earlier⁴ and modified by subsequent experience.⁵ It is a simple, general method for the synthesis of an N,N-dialkylnerylamine from isoprene and a dialkylamine. N,N-Dialkylnerylamines can also be prepared by the reaction of a dialkylamine with neryl chloride⁶ by a modification of Sandler's method.⁷ However, pure nerol, the starting material of neryl chloride, is expensive, and not easily available commercially. The present method illustrates a mild and convenient one-step reaction for the preparation of an N,N-dialkylnerylamine. In addition, the starting materials are readily accessible, the reaction proceeds stereoselectively, and the yields of the product are generally high. This process consists of the initial addition of lithium dialkylamide to isoprene, followed by the propagation of the resulting intermediate, and the termination by dialkylamine.

N,N-Dialkylnerylamines serve as convenient precursors for naturally occurring acyclic monoterpenes such as linalool,⁸ citronellal,⁹ and citral.¹⁰

1. Department of Synthetic Chemistry, Faculty of Engineering, Shizuoka University, Johoku, Hamamatsu 432 Japan.
2. Chalk, A. J.; Magennis, S. A.; Wertheimer, L. V. In "Fundamental Research In Organometallic Chemistry", Tsutsui, M.; Ishii, Y.; Yaozeng, H., Eds.; Van Nostrand Reinhold: New York, 1982; p. 851.
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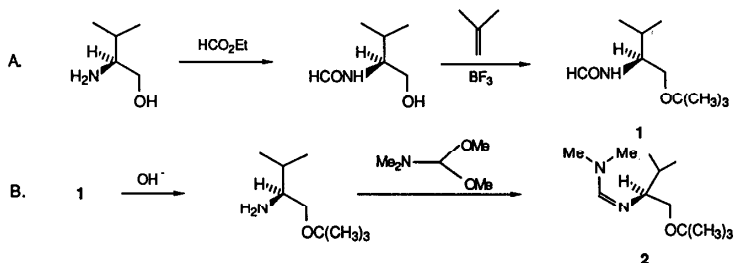
Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

N,N-Diethylnerylamine: 2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, (Z)-
(9); (40137-00-6)

(S)-N,N-DIMETHYL-N'-(1-tert-BUTOXY-3-METHYL-2-BUTYL)FORMAMIDINE
(Methanimidamide, N'-[1-[(1,1-dimethylethoxy)methyl]-
2-methylpropyl]-N,N-dimethyl-, (S)-)



Submitted by Daniel A. Dickman, Michael Boes, and Albert I. Meyers.¹

Checked by Jeffrey Romine and Leo A. Paquette.

1. Procedure

A. *(S)-N-Formyl-O-tert-butylvalinol* (1). In a 100-mL, round-bottomed flask, 20.6 g (200 mmol) of (S)-valinol (Note 1) and 16 g (216 mmol) of ethyl formate (Note 2) are heated at reflux under a nitrogen atmosphere for 1 hr. Excess ethyl formate is removed under reduced pressure and the oil is triturated with dry ether until a yellow solid appears. This material is dissolved in 260 mL of dry dioxane (Note 3) in a 1000-mL pressure bottle (Note 4) which is equipped with a magnetic stirring bar and is immersed in an ice-water bath. The bottle is immediately charged with ca. 260 mL of liquid isobutene (Note 5) and 75 mL of boron trifluoride etherate is rapidly added.

The pressure bottle is sealed with a stopper, removed from the ice bath, and stirred at room temperature for 3 hr (Note 6). In a fume hood, excess isobutene is removed from the resulting clear solution by carefully cracking the seal of the stopper. When the gas ceases to discharge, the stopper is removed and the solution is poured into a 1000-mL separatory funnel containing 250 mL of 2 N sodium hydroxide and is extracted twice with 100 mL of dichloromethane. The organic layer is washed with 100 mL of brine and dried over anhydrous magnesium sulfate. The organic solvent is removed and the residue is distilled (Kugelrohr tube, 0.05 mm, 80-85°C bath temperature) to give 27-36 g (75-95%) of N-formyl-O-tert-butylvalinol (1) as a clear oil (Note 7).

B. (S)-N,N-Dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine (2).

In a 500-mL, round-bottomed flask 26 g (140 mmol) of the formamide from Part A is dissolved in 100 mL of ethanol and 200 mL of a 50% aqueous potassium hydroxide solution is added. The mixture is heated at reflux overnight; upon cooling, the reaction separates into colorless aqueous and organic layers. The two layers are extracted three times with 100 mL of ether and the combined organic layers are washed with 100 mL of brine. After the solution is dried over anhydrous potassium carbonate and filtered, the ether and ethanol are carefully removed under aspirator vacuum at ambient temperature. The crude amine is treated with 25 g (210 mmol) of N,N-dimethylformamide dimethyl acetal (Note 8) and the reaction mixture is heated under argon at 40°C for 1 hr. The solution is concentrated under reduced pressure and the crude product is distilled bulb-to-bulb (0.05 mm, 55-65°C) to give 25.7-27 g (86-91.5%) of (S)-N,N-dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine (2) as a colorless liquid (Note 9).

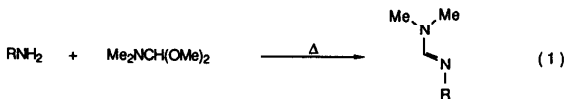
2. Notes

1. (L)- or (S)-Valinol was purchased from Aldrich Chemical Company, Inc. and used without further purification. The preparation of (L)-valinol has been described: Smith, G. A.; Gawley, R. E. *Org. Synth.* **1985**, *63*, 136.
2. Ethyl formate was purchased from J. T. Baker Chemical Company.
3. Dioxane was distilled from lithium aluminum hydride.
4. A Kimble bottle (#15096) purchased from VWR Scientific (Cat. no. 16267-101) was employed.
5. Isobutene was purchased from Matheson Gas Products.
6. The two-layer system became a clear solution within 15 min.
7. The physical properties are as follows: IR (neat) cm^{-1} : 3300, 1660; ^1H NMR (CDCl_3 , 300 MHz) δ : 0.79-0.88 (m, 6 H), 1.07 (s, 9 H), 1.82 (m, 1 H), 3.3 (m, 2 H), 3.75 (m, 1 H), 7.94 (d, 1 H, $J = 12$), 8.13 (d, 1 H, $J = 1$); $[\alpha]_D^{25} -59.6^\circ$ (EtOH, c 3.5).
8. N,N-Dimethylformamide dimethyl acetal was purchased from Aldrich Chemical Company, Inc.
9. The physical properties are as follows: IR (neat) cm^{-1} : 1660; ^1H NMR (CDCl_3 , 300 MHz) δ : 0.77 (d, 3 H, $J = 6.5$), 0.79 (d, 3 H, $J = 6.5$), 1.07 (s, 9 H), 1.72 (m, 1 H), 2.6-3.5 (m, 3 H), 2.73 (s, 6 H), 7.14 (s, 1 H); $[\alpha]_D^{25} -15.9^\circ$ (THF, c 0.98).

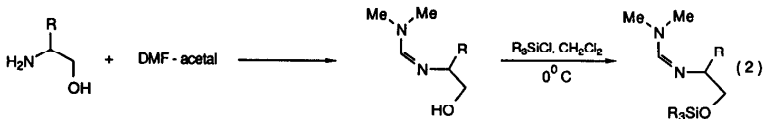
3. Discussion

This procedure for the synthesis of N,N-dimethyl-N'-alkylformamidines is representative for both chiral and achiral alkyl groups. These compounds are used to activate a wide range of secondary amines toward metalation and alkylation and may be removed to furnish the α -alkylated amines.²

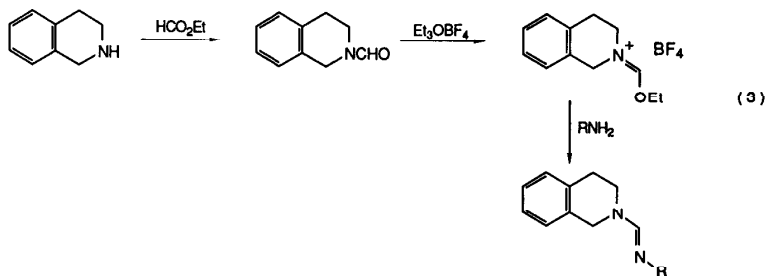
N,N-Dimethyl-N'-alkylformamidines may be prepared from dimethylformamide dimethyl acetal and a primary amine by heating for 1-5 hr³ (eq. 1, Table I).



It is also possible to simply heat "DMF-acetal" with an amino alcohol (e.g. valinol, leucinol, etc.) and obtain the hydroxy formamidine which can be directly silylated with Et_3SiCl , Me_3SiCl , or $t\text{-BuMe}_2\text{SiCl}$ at 0°C in dichloromethane (eq. 2).^{2a} If these N,N-dimethylformamidines are required, this procedure has the advantage of eliminating the sometimes troublesome cleavage of a silyl ether during reaction with DMF-acetal.



In addition to the exchange reaction⁴ described previously,⁵ formamidines derived from secondary amines can be prepared by forming the N-formyl derivative, which is treated successively with boron trifluoride etherate and the appropriate primary amine^{2a} (eq. 3, Table II). However, this method is not satisfactory if sensitive groups (e.g., Me₃Si) are present on the amine since they are cleaved by the Meerwein reagent.



The main advantages of using the tert-butyl ether of the valinol formamidine are its stability to reaction conditions used in the asymmetric alkylation of amines and its ready recovery from these reactions for further use.

TABLE I

PREPARATION OF N, N-DIMETHYL-N'-ALKYLFORMAMIDINES

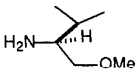
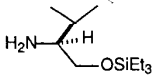
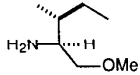
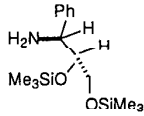
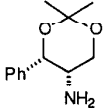
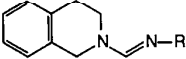

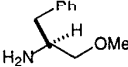
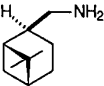
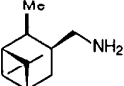
RNH_2	% yield
	95
	98
	90
	96
	98

TABLE II

PREPARATION OF FORMAMIDINES VIA N-FORMYL DERIVATIVES

RNH ₂	(%)	
	98	
	94	
	98	
	97	

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523.
2. (a) Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361:
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S) N,N Dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine:
Methanimidamide, N'-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-
N,N-dimethyl-, (S)- (11); (90482-06-7)

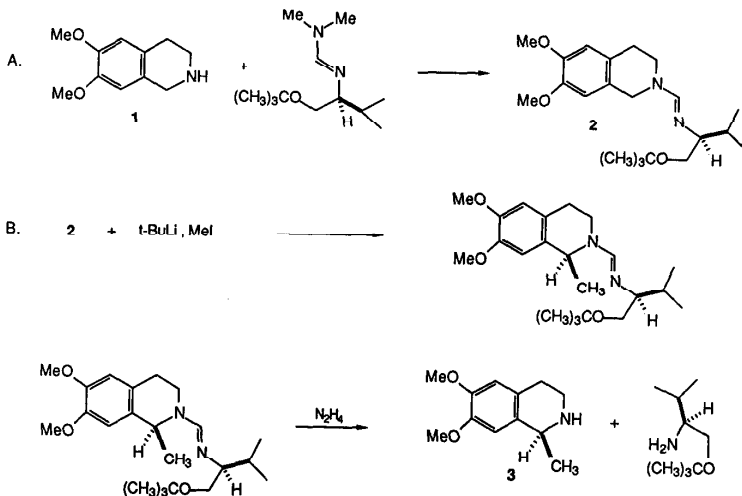
(S)-N-Formyl-O-tert-butylvalinol: Formamide, N-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-, (S)- (11); (90482-04-5)

Valinol: 1-Butanol, 2-amino-3-methyl-, L (8); 1-Butanol, 2-amino-3-methyl-, (S)- (9); (2026-48-4)

N,N-Dimethylformamide dimethyl acetal: Trimethylamine, 1,1-dimethoxy- (8);
Methanamine, 1,1-dimethoxy-N,N-dimethyl- (9); (4637-24-5)

(-)-SALSOLIDINE

(Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-, (S)-)



Submitted by Albert I. Meyers,¹ Michael Boes, and Daniel A. Dickman.

Checked by Melinda Gugelchuk and Leo A. Paquette.

1. Procedure

A. *6,7-Dimethoxy-1,2,3,4-tetrahydro-2-[(1-tert-butoxy-3-methyl)-2-butyl-1-iminomethyl]isoquinoline (2)*. In a 250-mL, round-bottomed flask 10.0 g (51.7 mmol) of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 1 (Note 1) is combined

with 11.5 g (53.7 mmol) of (S)-N,N-dimethyl-N'-(1-tert-butoxy-3-methyl)-2-butylformamidine (Note 2), 50 mL of dry toluene and 50 mg of (+)-camphor-sulfonic acid (Note 3). The mixture is heated to reflux for 24 hr and allowed to cool to room temperature. Approximately 30 mL of toluene is removed by rotary evaporation and the residual solution is heated at reflux for an additional 2 days. After the reaction mixture is cooled, it is diluted with 50 mL of dichloromethane and washed with 50 mL of 1 N sodium hydroxide and 100 mL of brine and the organic layer is dried over anhydrous potassium carbonate, filtered, and concentrated by rotary evaporation. The residue is distilled (Kugelrohr 0.1 mm, 170°C bath temp) to give 18.0 g (96%) of 2 as a pale yellow oil (Note 4).

B. (S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, (-)-salsolidine (3). A 500-mL, three-necked flask, containing a magnetic stirring bar, is equipped with a three-way stopcock, low temperature thermometer, and a rubber septum. The flask is charged with 15.0 g (41.4 mmol) of formamidine 2, filled with argon, and kept under a pressure of ca. 100 mm against the atmosphere (Note 5). Through the septum, via a syringe, is added 300 mL of dry tetrahydrofuran (Note 6) and the solution is cooled to -75°C in a dry ice-acetone bath. A tert-butyllithium solution (21 mL of a 2.4 M solution, Note 7), is added dropwise within 5 min through the septum. After the solution is stirred at -75°C for 45 min, the deep red solution is cooled to -100°C in a liquid nitrogen-methanol bath and, after 15 min at -100°C, 3 mL of freshly distilled iodomethane (Note 8) dissolved in 10 mL of dry tetrahydrofuran is added by syringe at such a rate that the temperature of the reaction mixture does not rise above -90°C. Stirring is continued for 3 hr and the solution is poured into a 1-L separatory funnel containing 50 mL of water. This is extracted twice with 100 mL of dichloromethane and the combined organic layers

are washed with 100 mL of brine, dried over potassium carbonate, and filtered. Removal of the solvent on a rotary evaporator gives a cloudy yellow oil, which is dissolved in 100 mL of 60% ethanol. To this solution is added 4.5-5.0 mL of hydrazine (Note 9) followed by 3.0 mL of glacial acetic acid (pH 8-9). The mixture is stirred overnight at ambient temperature and diluted with 50 mL of water. It is extracted twice with 100 mL of dichloromethane and the combined organic extracts are washed with 50 mL of water, dried (potassium carbonate), filtered and concentrated at *ambient temperature under aspirator pressure*. The residue, which consists of valinol tert-butyl ether and salsolidine, is distilled bulb-to-bulb under aspirator pressure at 105°C (pot temperature). This removes the valinol tert-butyl ether (Note 10), leaving crude salsolidine as the pot residue. The residue is dissolved in 100 mL of ether and washed twice with 35-mL portions of ice water - 3 N hydrochloric acid (1:4). The ether layer is discarded and the acidic aqueous layer is neutralized with cold (0-5°C) aqueous 25% sodium hydroxide until it is alkaline to pH paper. The creamy mixture is immediately extracted twice with 50 mL of dichloromethane and the organic layers are drawn off, combined, and dried over anhydrous potassium carbonate. After the drying agent is removed by filtration, it is washed twice with 5 mL of dichloromethane. The filtrate and wash are concentrated by rotoevaporation, leaving a yellow oil. Distillation (Kugelrohr) at a pot temperature of 120-125°C (0.01 mm) gives 5.1-5.3 g (60-63%) of (S)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (salsolidine) 3 as a pale yellow oil, which crystallizes on standing (Note 11), mp 47-49°C, (Notes 12 and 13).

2. Notes

1. The tetrahydroisoquinoline was purchased from Aldrich Chemical Company, Inc. and treated with aqueous 5% sodium hydroxide, extracted with dichloromethane, dried over sodium sulfate and distilled, bulb-to-bulb at 0.01 mm (58-60°C, bath temp) to give a colorless oil. The compound solidifies to give an amorphous solid: mp 83.0-84.5°C; ^1H NMR (CDCl_3 , 300 MHz) δ : 2.30 (br s, 1 H), 2.69, (t, 2 H, $J = 6$), 3.12 (t, 2 H, $J = 6$), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.95 (s, 2 H), 6.50 (s, 1 H), 6.58 (s, 1 H).

2. See the previous procedure for preparation of this chiral formamidine; *Org. Synth.* **1988**, 67, 52.

3. (+)-10-Camphorsulfonic acid was purchased from Aldrich Chemical Company, Inc.

4. The physical properties are as follows: ^1H NMR (CDCl_3 , 300 MHz) δ : 0.87 (d, 3 H, $J = 6.8$), 0.87 (d, 3 H, $J = 6.7$), 1.14 (s, 9 H), 1.83 (hept, 1 H, $J = 7$), 2.68-2.81 (m, 3 H), 3.20 (dd, 1 H, $J_1 = 8.8$, $J_2 = 7.1$), 3.43-3.56 (m, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.40 (AB, 1 H, $J = 17$), 4.43 (AB, 1 H, $J = 17$), 6.60 (s, 1 H), 6.63 (s, 1 H), 7.40 (s, 1 H); $[\alpha]_D^{25} -30.3^\circ$ (CHCl_3 , c 2.7).

5. The flask was filled with argon by evacuating and pressurizing several times through the three-way stopcock.

6. Tetrahydrofuran was distilled from sodium wire and benzophenone.

7. *tert*-Butyllithium solution in pentane was purchased from Alfa Products, Morton/Thiokol Inc.

8. Iodomethane was purchased from Aldrich Chemical Company, Inc.

9. Anhydrous hydrazine was purchased from Aldrich Chemical Company, Inc.

10. The spectral properties are as follows: ^1H NMR (CDCl_3) δ : 0.92 (d, 6 H, $J = 6$), 1.19 (s, 9 H), 1.61 (m, 1 H), 2.64 (m, 1 H), 3.12 (overlapping doublets, 1 H, $J = 8$, $J = 9$), 3.40 (dd, 1 H, $J = 8$, $J = 9$).

11. The checkers did not observe crystallization at this point when the reaction was run on a much smaller scale (8 mmol). Two runs, each starting with 3.05 g of 2, gave rise to 0.88 g (51%) and 0.83 g (46%) of purified (-)-salsolidine.

12. The physical properties are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.41 (d, 3 H, $J = 6.6$), 1.78 (br s, 1 H), 2.65 (m, 1 H), 2.77 (m, 1 H), 3.01 (m, 1 H), 3.25 (m, 1 H), 3.822 (s, 3 H), 3.828 (s, 3 H), 3.89 (m, 1 H), 6.61 (s, 1 H), 6.55 (s, 1 H); $[\alpha]_D^{22}$ -53.9 to -54.0° ($\text{C}_2\text{H}_5\text{OH}$, c 3.8) (lit.² -59.5° \pm 0.5°); (95-96% ee by Pirkle HPLC analysis, Note 13).

13. Enantiomeric purity determination was performed as follows: The (-)-salsolidine 3 (100 mg) was dissolved in 1 mL of dichloromethane and 0.05 mL of triethylamine. To this solution was added 150 mg of 1-naphthoyl chloride (Aldrich Chemical Company, Inc.) and the reaction mixture was stirred for 0.5 hr at room temperature, then poured into 5 mL of aqueous 20% sodium hydroxide solution. Extraction with 10 mL of dichloromethane was followed by separation of the organic layer which was dried over potassium carbonate. The solvent was removed under reduced pressure and the crude naphthamide was purified by column chromatography on silica gel (ethyl acetate-hexane-dichloromethane, 1:4:5). Enantiomeric analysis was performed using a Waters Associates Model 440 high pressure liquid chromatograph equipped with a Pirkle Covalent Phenylglycine Column (Baker Bond Chiral HPLC Column, DNBPG, J. T. Baker, Phillipsburg, NJ). The detector used was UV at 254 nm and the solvent for elution was 10% 2-propanol-hexane at 5 mL/min with a back pressure of 3500 psi. The peaks were baseline separated and electronically integrated.

3. Discussion

This method of asymmetric alkylation has been performed in a number of other systems with equally good enantioselectivity. Tetrahydroisoquinolines have been alkylated³ (Eq 1) with various alkyl halides to give 1-substituted tetrahydroisoquinolines in 50-70% overall yields and with excellent ee's. Several naturally occurring isoquinoline alkaloids have also been prepared (compounds A-C) in 95-98.5% ee.⁴ A number of chiral auxiliaries other than the valine-based tert-butyl ether also have been examined and gave 80-99% ee's after alkylation.⁵ However, the authors consider the chiral auxiliary used in the present procedure to be superior to the others.

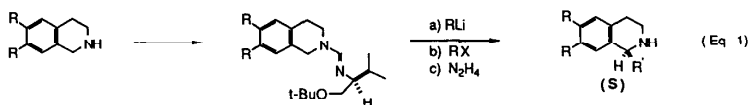
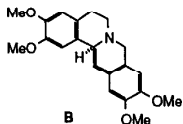


TABLE I

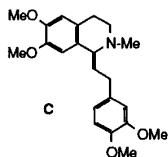
<u>R, R</u>	<u>R'X</u>	<u>% ee</u>
H	MeI	99
H	n-BuI	96
H	Allyl Br	96
H	PhCH ₂ Cl	98
MeO, MeO	3,4-(MeO) ₂ PhCH ₂ Br	99
MeO, MeO	3,4-(MeO) ₂ PhCH ₂ CH ₂ I	95



A



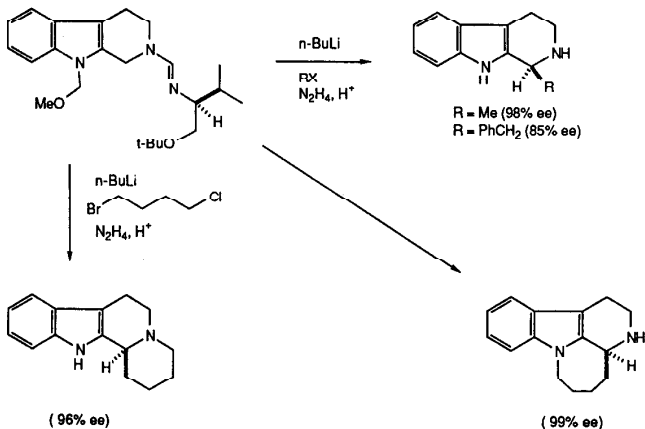
B



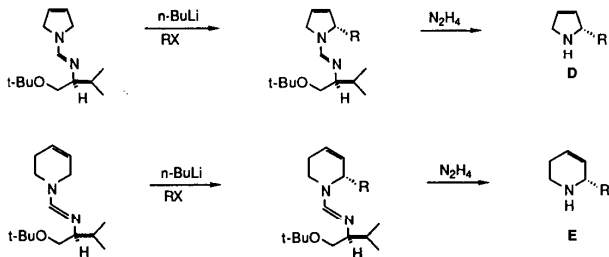
C

In addition to isoquinolines, β -carbolines have been used to afford indole alkaloids, both natural and unnatural (Scheme 1) in high enantiomeric excess.⁶ The indole nitrogen is protected as the methoxymethyl ether and later removed to provide the unsubstituted indole. In the absence of indole-nitrogen protection, the potassium-salt is satisfactory but results in low asymmetric induction. However, if racemic products are desired, *N*-*tert*-butyl-formamidines can be used,⁷ and smooth alkylation of the α -protons is achieved, thus obviating the need for protection of the indole nitrogen.

Scheme 1



Asymmetric alkylations also are feasible, leading to the chiral dihydropyrrole (D) and the tetrahydropiperidine systems (E).⁸ When the



saturated analogs were employed (pyrrolidine and piperidine), no metallation could be effected in the presence of the chiral auxiliary, although metallation-alkylation proceeded normally when the N-tert-butylformamidines were employed.

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

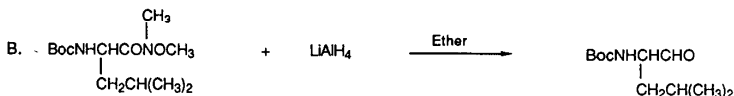
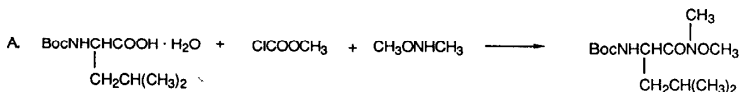
(-)-Salsolidine: Salsolidine (8); Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-, (S)- (9); (493-48-1)

6,7-Dimethoxy-1,2,3,4-tetrahydro-2-[(1-tert-butoxy-3-methyl)-2-butylimino-methyl]isoquinoline: Isoquinoline, 2-[[[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]imino]methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, (S)- (11); (90482-03-4)

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride: Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-, hydrochloride (8,9); (2328-12-3)

(S)-N,N-Dimethyl-N'-(1-tert-butoxy-3-methyl-2-butyl)formamidine: Methanimidamide, N'-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-N,N-dimethyl-, (S)- (11); (90482-06-7)

N-tert-BUTOXYCARBONYL-L-LEUCINAL
 (Carbamic acid, (1-formyl-3-methylbutyl)-,
 1,1-dimethylethyl ester, (S)-)



Submitted by O. P. Goel, U. Krolls, M. Stier, and S. Kesten.¹

Checked by Susumu Ohira and James D. White.

1. Procedure

A. Boc-L-Leucine N-methyl-O-methylcarboxamide. A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, an electronic digital thermometer, and a graduated addition funnel. The flask is charged with 39.1 g (0.4 mol) of N,O-dimethylhydroxylamine hydrochloride (Note 1) and 236 mL of methylene chloride (Note 2). The suspension is stirred and cooled to 2°C with an ice-water bath. N-Methylpiperidine (Note 3), 48.8 mL (0.41 mol), is placed in the addition funnel and added dropwise while the temperature is maintained at 2° ± 2°C. A clear, colorless solution results which is kept cold and used in the following reaction.

A 5-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, thermometer, and an addition funnel with drying tube. The flask is charged with 100 g (0.4 mol) of Boc-L-leucine hydrate (Note 4), 458 mL of tetrahydrofuran (Note 2), and 1.8 L of methylene chloride. A clear solution results on stirring, which is cooled to $-20^{\circ} \pm 2^{\circ}\text{C}$ by immersing the flask in a dry ice-2-propanol bath. N-Methylpiperidine, 48.8 mL (0.41 mol), is placed in the addition funnel and added rapidly to the mixture, while the temperature is allowed to rise to $-12^{\circ} \pm 2^{\circ}\text{C}$. Methyl chloroformate (Note 5), 31 mL (0.4 mol) is then placed in the addition funnel and added rapidly to the mixture with good stirring, while the temperature is kept at $-12^{\circ} \pm 2^{\circ}\text{C}$. Two minutes later the solution of N,O-dimethylhydroxylamine, prepared as described earlier, is added. The cooling bath is removed and the clear solution allowed to warm to room temperature over 4 hr (Note 6). The solution is again cooled to 5°C and extracted with two 500-mL portions of aqueous 0.2 N hydrochloric acid and two 500-mL portions of aqueous 0.5 N sodium hydroxide (Note 7). The solution is washed with 500 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated on a rotary evaporator at a bath temperature of $30\text{--}35^{\circ}\text{C}$. The residue is further evacuated on an oil pump to constant weight. The residual colorless syrup weighs 100-102 g (91-93%), $[\alpha]_{\text{D}}^{23} -24$ to -25° (1.5% in methanol) (Note 8).

B. *N-tert-Butoxycarbonyl-L-leucinal: Boc-L-leucinal.* A 5-L, four-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, a thermometer, a pressure-equalizing addition funnel, and an air-cooled condenser fitted with an argon blanket adapter. The flask is charged under an argon blanket with 17.7 g (95% pure, 0.44 mol) of lithium aluminum hydride (Note 9), and 1.5 L of anhydrous ethyl ether (Note 10). The grey suspension is stirred at room temperature for 1 hr or until most of the solid is finely

dispersed. The flask is immersed in a dry ice-2-propanol bath and the suspension cooled to -45°C . A solution of the Boc-L-leucine N-methyl-O-methylcarboxamide, obtained in Part A, in 300 mL of anhydrous ethyl ether is placed in the addition funnel and added to the lithium aluminum hydride suspension in a steady stream (Note 11) while the reaction temperature is maintained $-35^{\circ} \pm 3^{\circ}\text{C}$. The cooling bath is removed and the mixture is stirred and allowed to warm to $+5^{\circ}\text{C}$. The mixture is once again cooled to -35°C and a solution of 96.4 g (0.71 mol) of potassium bisulfate (Note 12) in 265 mL of deionized water is placed in the addition funnel. This is added cautiously at first and then rapidly, while the temperature is allowed to rise to $-2^{\circ} \pm 3^{\circ}\text{C}$. The cooling bath is removed and the mixture stirred for 1 hr. The reaction mixture is filtered through a 2" pad of Celite (Note 13). The filter cake is washed with two 500-mL portions of ethyl ether. The combined ether layers are washed in sequence with three 350-mL portions of cold (5°C) 1 N hydrochloric acid, two 350-mL portions of saturated aqueous sodium bicarbonate solution, and 350 mL of saturated sodium chloride solution. The organic solution is dried over magnesium sulfate and evaporated on a rotary evaporator (bath at 30°C). The residual, slightly cloudy syrup weighs 69-70 g (87-88%), $[\alpha]_D^{23}$ -49 to -51° (1.65% in methanol) (Note 14). The product is stored in a freezer (-17°C) prior to use. It solidifies readily at 5°C (Note 15).

2. Notes

1. N,O-Dimethylhydroxylamine hydrochloride was obtained from the Aldrich Chemical Company, Inc., and used as received.

2. Methylene chloride and tetrahydrofuran were obtained from the Fisher Scientific Company.

3. N-Methylpiperidine was obtained from the Aldrich Chemical Company, Inc., and used as received.

4. Bachem Inc. was the source of Boc-L-leucine hydrate. It was not necessary to prepare anhydrous Boc-L-leucine. The yield and quality of the product were unaffected by the presence of water during the reaction.

5. Methyl chloroformate was obtained from the Aldrich Chemical Company, Inc.

6. The reaction mixture may be stirred overnight for convenience.

7. The organic solution should be kept at 5° to 15°C during extractions.

8. The crude product is 96-99% pure by HPLC and is satisfactory for use in the next reaction. HPLC was carried out on a Varian 5500 instrument using a 250 cm x 4.6 mm I.D. Alltech C-18 column with 60:40 methanol:0.5 M $\text{NH}_4\text{H}_2\text{PO}_4$ (pH 3) as the mobile phase, UV detector at 210 nm. Thin layer chromatography on silica gel plates (EM) and development with hexane:EtOAc(3:1) indicates that the major product spot is at $R_f = 0.32$. Starting Boc-L-leucine, if present, appears at $R_f = 0.16$; detector: ninhydrin and gradual warming on a hot plate. The physical properties are as follows: IR (liquid film) cm^{-1} : 2960(s), 1714(s), 1665(s); ^1H NMR (200 MHz, CDCl_3) δ : 0.92 (2d appear as t, 6 H, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$), 1.40 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.38-1.44 (m, 2 H, $\text{C}_3\text{-H}$), 1.59-1.76 (m, 1 H, $\text{C}_4\text{-H}$), 3.17 and 3.14 (s and a rotamer singlet, 3 H, N-CH_3), 3.76 and 3.67 (s, and a rotamer singlet, 3 H, O-CH_3), 4.7 (m, 1 H, $\text{C}_2\text{-H}$), 5.06 (m, 1 H, N-H).

9. Lithium aluminum hydride was obtained from Alfa Products, Morton/Thiokol Inc.

10. Ethyl ether was obtained from the Fisher Scientific Co.

11. The lithium aluminum hydride suspension should be cooled to -45°C prior to addition of the amide. Higher initial temperatures (-30°C and above) lead to an impurity as shown by TLC.

12. Potassium bisulfate was obtained from the Matheson, Coleman and Bell Co. A saturated aqueous solution is obtained after stirring overnight. Aqueous potassium bisulfate will react vigorously if tetrahydrofuran is the reaction medium in place of ethyl ether.

13. A gel-like precipitate is formed from the inorganic by-products. A thick Celite pad helps to prevent clogging of the filter funnel.

14. Consistently higher optical rotations than reported were obtained.² NMR and capillary gas chromatographic analyses indicated chemical purity of 98 to 99%. Varian 6000, RSL-310, 15 meter, fused silica column, 0.25 mm ID, film thickness 0.25 μm , at 60°C for 4 min and then 60 - 220°C at $10^{\circ}\text{C}/\text{min}$, H_2 as carrier gas at 10 psi. TLC under the conditions described in Note 8 shows the major spot at $R_f = 0.53$. The spectral properties are as follows: IR (liquid film) cm^{-1} : 2961(s), 1736(s), 1698(b); ^1H NMR (200 MHz, CDCl_3) δ : 0.96 (d, 6 H, $J = 6.4$, $\text{CH}(\text{CH}_3)_2$), 1.45 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.48-1.81 (m, 3 H, $\text{C}_3\text{-H}$, $\text{C}_4\text{-H}$); 4.24 (m, 1 H, $\text{C}_2\text{-H}$); 4.92 (broad singlet, 1 H, N-H); 9.59 (s, 1 H, $\text{C}_1\text{-H}$).

15. Boc-L-Leucinal racemizes if stored at room temperature. Although it solidified in the cold it became liquid at room temperature. It is very soluble in pentane at room temperature, but crystallizes from it at -30°C . It is reported² to melt at 63 - 66°C .

3. Discussion

Boc-L-Leucinal is a useful chiral synthon in the preparation of the natural amino acid statine³ [S-(R*,R*)]-4-amino-3-hydroxy-6-methylheptanoic acid (3S,4S). The procedure reported here is based on the method of Fehrentz and Castro² for the preparation of optically active Boc amino aldehydes from α -amino acids. It is satisfactory on a kilogram scale. Boc-L-Leucinal has also been prepared by the reduction of Boc-L-leucine methyl ester with diisobutylaluminum hydride⁴ or by oxidation of Boc-L-leucinol.⁵ The reaction conditions described here differ from those in the literature.² The N-methoxy-N-methylamide is prepared simply and in high yield by the mixed anhydride method⁶ rather than with the very expensive reagent benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. In addition, the amide can be added to a cold lithium aluminum hydride suspension rather than inversely as recommended.² This is an important consideration for scale-up. Reduction of this amide with bis(2-methoxyethoxy)aluminum hydride solution (Red-Al) gave a substantially impure aldehyde.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-tert-Butoxycarbonyl-L-leucinal: Carbamic acid, (1-formyl-3-methylbutyl)-, 1,1-dimethylethyl ester, (S)- (9); (58521-45-2)

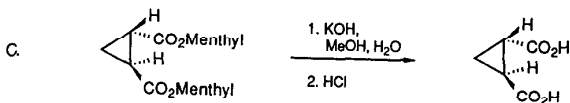
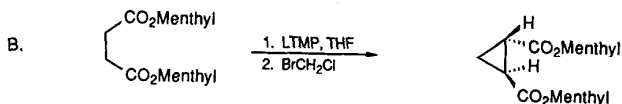
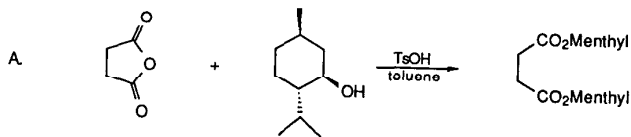
N-tert-Butoxycarbonyl-L-leucine N-methyl-O-methylcarboxamide: Carbamic acid, [1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester (S); (11); (87694-50-6)

N,O-Dimethylhydroxylamine hydrochloride: Methylamine, N-methoxy-, hydrochloride; (8); Methanamine, N-methoxy-, hydrochloride (9); (6638-79-5)

N-Methylpiperidine: Piperidine, 1-methyl- (8,9); (626-67-5)

N-tert-Butoxycarbonyl-L-leucine hydrate: Leucine, N-carboxy-, N-tert-butyl ester, L- (8); L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]- (9); (13139-15-6)

**CONDENSATION OF (-)-DIMENTHYL SUCCINATE DIANION WITH
1, ω -DIHALIDES: (+)-(1S,2S) CYCLOPROPANE 1,2 DICARBOXYLIC ACID
(1,2-Cyclopropanedicarboxylic acid, (1S,1S)-(+)-)**



Submitted by Kyoji Furuta, Kiyoshi Iwanaga, and Hisashi Yamamoto.¹

Checked by Ichiro Mori and Clayton H. Heathcock.

1. Procedure

A. *(-)-Dimenthyl succinate*. A 300-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap, and a reflux condenser. The flask is charged with 20 g (0.2 mol) of succinic anhydride,

62.5 g (0.4 mol) of *l*-menthol, 250 mg (1.3 mmol) of *p*-toluenesulfonic acid monohydrate, and 150 mL of toluene (Note 1). The mixture is heated under reflux in an oil bath (about 140°C) for 24 hr. During this period the theoretical amount of water (3.6 mL) is collected. The mixture is allowed to cool to ambient temperature, diluted with 200 mL of hexane, and poured into a mixture of 250 mL of aqueous saturated sodium bicarbonate, 100 mL of methanol, and 200 mL of water. The organic phase is separated and the aqueous phase is extracted twice with 100 mL of hexane. The organic phases are combined, washed once with 200 mL of saturated brine, and dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is dissolved in 100 mL of methanol. After the solution stands in a refrigerator overnight, colorless crystals appear in the mixture and are collected by filtration with suction (Note 2). This material (ca. 70 g in two crops) is purified by recrystallization from methanol to afford 66 g (84%) of pure (-)-dimenthyl succinate, mp 63-64°C (Note 3).

B. (-)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate. A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL, pressure-equalizing dropping funnel, rubber septum, and a three-way stopcock with a nitrogen inlet. The air in the system is replaced with dry nitrogen. The flask is charged with 180 mL of dry tetrahydrofuran and cooled with an ice bath; 14.1 mL of a 1.1 M hexane solution of butyllithium (126 mmol) (Note 4) is added. This solution is stirred while 21.3 mL (126 mmol) of 2,2,6,6-tetramethylpiperidine (Note 5) is added dropwise with a syringe through the septum over a 10-min period. The resulting solution of lithium 2,2,6,6-tetramethylpiperidide (LTMP) is cooled to -78°C with a dry ice-methanol bath (Note 6) and stirred. A solution of 23.7 g (60 mmol) of (-)-dimenthyl succinate in 50 mL of dry tetrahydrofuran is

then added dropwise through the addition funnel over a period of 1 hr. The wall of the funnel is rinsed with 10 mL of dry tetrahydrofuran and the rinse is added to the solution. The resulting yellow solution of succinate dianion is stirred for 1 hr. To the solution is added dropwise 3.9 mL (60 mmol) of bromochloromethane (Note 7) with a syringe through the septum over a 10-min period. After the reaction mixture is stirred for 2 hr (Note 8), 2.2 mL (24 mmol) of isobutyraldehyde (Note 9) is added dropwise to quench any unreacted anions (Note 10). After being stirred for an additional 30 min, the reaction mixture is poured into 250 mL of ice-cooled 1 N hydrochloric acid and the product is extracted three times with 150 mL of ether. The combined organic phases are washed with 250 mL of brine, dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The residue is chromatographed on 700 g of silica gel (Note 11) packed in a 9.5-cm diameter column using a mixture of ether and hexane (1:18) as eluant. The appropriate fractions are collected and concentrated to give 11.5 g (47%) of (-)-dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate as colorless crystals. Analysis by GC indicates a diastereomeric ratio of 96:4 (Note 12). Recrystallization of this material from 25 mL of methanol affords 9-10 g (38-40%) (Note 13) of optically pure product, mp 95-96°C (Note 14).

C. (+)-(1S,2S)-Cyclopropane-1,2-dicarboxylic acid. (-)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate (4.06 g, 10 mmol, $[\alpha]_D^{25} +17.8^\circ$) is dissolved in 20 mL of a 10% potassium hydroxide solution in 9:1 methanol/water in a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar. The solution is heated at 60°C with an oil bath. Progress of the reaction is monitored by TLC on silica gel, using 1:1 hexane/ethyl acetate as eluant (Note 15). After about 4 hr the resulting two-phase mixture is diluted with 20 mL of water and extracted with three 40-mL portions of ether (Note

16). The aqueous layer is acidified by the addition of 20 mL of ice-cold 6 N hydrochloric acid, saturated with ca. 5 g of sodium chloride, and extracted with five 40-mL portions of ether. The combined organic layers are dried over sodium sulfate, diluted with 5 mL of hexane, and concentrated with a rotary evaporator. Filtration provides 1.17 g (90%) of (+)-(1S,2S)-cyclopropane-1,2-dicarboxylic acid, mp 172-173°C, $[\alpha]_D^{25} +220^\circ$ (ethanol, c 1.01) [lit.² mp 169.5-170°C, $[\alpha]_D^{25} +227.9^\circ$ (ethanol, c 2.342)] (Note 17).

2. Notes

1. Succinic anhydride and p-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Guaranteed-grade L-(-)-menthol was purchased from Tokyo Kasei Kogyo Company, Ltd. (Japan). Reagent-grade toluene was dried and stored over sodium metal. The checkers obtained p-toluenesulfonic acid from Eastman Kodak, and succinic anhydride and L-(-)-menthol from the Aldrich Chemical Company, Inc.

2. In the first trial the checkers experienced difficulty in crystallization at this point, even after keeping the solution in a 5°C-refrigerator for four days. Crystallization was induced by cooling the crude product (ca. 80 g of oil) to -78°C in a methanol-dry ice bath. Ether (5 mL) was added to the resulting glass, the cooling bath was removed, and the surface of the solid material was scratched continuously with a spatula. At about 0°C the glass began to melt and small white spots appeared. Continued stirring of the viscous material as it warmed resulted in crystallization of the entire mass. The crystalline mass was dried under vacuum and a small portion kept as seed crystals. The remainder was dissolved in 100 mL of warm methanol. After the solution was cooled to room temperature, a small quantity

of the seed material was added and the solution was placed in a 5°C-refrigerator overnight. Approximately 68 g of crystalline (-)-dimenthyl succinate was obtained. The filtrate was condensed with a rotary evaporator and cooled again to give another 2.6 g. In subsequent trials, the foregoing procedure was not necessary as the crude diester crystallized spontaneously, giving a similar yield in two crops.

3. The submitters report mp 65-66°C. The physical properties are as follows: ^1H NMR (CDCl_3 , 250 MHz) δ : 0.70-2.02 (complex, 18 H), 0.75 (d, 6 H, $J = 6.9$), 0.89 (d, 12 H, $J = 6.4$), 2.60 (s, 4 H), 4.70 (dt, 2 H, $J = 4.4$, 10.8); $[\alpha]_D^{25} -88.7^\circ$ (CHCl_3 , c 1.02).

4. Tetrahydrofuran was freshly distilled from sodium-benzophenone. Butyllithium was obtained from Wako Pure Chemical Industries, Ltd. or Foote Mineral Company. It was titrated with anhydrous 2-butanol using 1,10-phenanthroline as an indicator.

5. 2,2,6,6-Tetramethylpiperidine, purchased from Tokyo Kasei Kogyo Company, Ltd. or Aldrich Chemical Company, Inc., was used. The use of this sterically-hindered lithium amide is crucial for high diastereoselectivity. If lithium diisopropylamide is used, the diastereoselectivity of the reaction is reduced significantly.³

6. The flask was cooled with a dry ice-methanol bath for 30 min before subsequent addition.

7. Bromochloromethane was purchased from Tokyo Kasei Kogyo Company, Ltd. or from Aldrich Chemical Company, Inc. and was used without purification.

8. TLC (ether-hexane) showed residual starting material.

9. Isobutyraldehyde was obtained from Wako Pure Chemical Industries, Ltd. or from Aldrich Chemical Company, Inc. and was used without purification.

10. This procedure was not essential but facilitated the subsequent chromatographic separation of desirable product from residue.

11. Silica gel (70-200 mesh) purchased from Fuji Davison Chemical (BW-820 MH) was used. The checkers used silica gel (230-400 mesh) purchased from Merck (Kieselgel 60).

12. GC analysis was performed with a capillary column (PEG, 0.25 mm x 25 m) purchased from Gaskuro Kogyo Company, Ltd. (Japan). The checkers used a 0.2 mm x 25 m Carbowax 20 M capillary column. The diastereomeric excess ranged from about 80 to 92%. In all cases, however, essentially pure material could be obtained by a subsequent single recrystallization. The diastereomeric ratio can be further improved by reducing the amount of added bromochloromethane. This may be due to the stereochemical purity of the enolates. On treatment with lithium 2,2,6,6-tetramethylpiperidide, the succinate affords mainly the E,E-enolate and only a slight amount of Z,Z-enolate; the latter may induce the opposite stereochemistry in the product. Fortunately, the E,E-enolate is more reactive, and therefore, the undesirable reaction with Z,Z-enolate can be suppressed kinetically by reducing the amount of halide. Thus the use of 0.5 equivalent of bromochloromethane compared to starting ester results in over 99% diastereoselectivity with comparable chemical yield, based on the halide. The procedure described in the text is, however, recommended from a practical point of view.

13. This yield ranges from 38 to 57% in several experiments. Recrystallization was accomplished by dissolving the crude diester in warm methanol and then allowing this solution to cool to room temperature. The checkers found that, if crystallization was induced by cooling the methanol solution in

a refrigerator, the crystalline diester was accompanied by an oily by-product. A second recrystallization was then necessary to purify the material.

14. The submitters report mp 99-100°C. The physical properties are as follows: ^1H NMR (CDCl_3 , 250 MHz) δ : 0.70-2.02 (complex, 20 H), 0.76 (d, 6 H, $J = 7.0$), 0.90 (d, 12 H, $J = 6.8$), 2.12. (dd, 2 H, $J = 7.4, 7.2$), 4.68 (dt, 2 H, $J = 5.4, 10.9$); $[\alpha]_D^{25.5} +17.8^\circ$ (CHCl_3 , c 1.0).

15. During the course of the saponification, a spot with R_f intermediate between that of the reactant and product (presumably the monoester) was observed.

16. The combined organic layer may be washed with 50 mL of brine, dried over sodium sulfate, and evaporated to recover 3.45 g of crude menthol.

17. The checkers note that in the paper by Inouye, et al.² the diacid was prepared by ozonolysis of (+)-trans-2-phenylcyclopropanecarboxylic acid having 96.3% optical purity. The product diacid was purified by sublimation and recrystallization from water to obtain material giving the cited physical properties. Although the original publication² claims an optical purity of 96.3% for this diacid, it is probably optically pure because of the recrystallization step.

3. Discussion

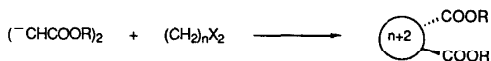
The procedure described here provides a simple and general method for the construction of optically active trans-cycloalkane-1,2-dicarboxylic acids.³ The reaction has been applied successfully to a series of dihalides and ditosylates (Table).

A few methods are described in the literature for the preparation of optically-active dialkyl trans-cyclopropane-1,2-dicarboxylates,² including a Michael addition-condensation sequence of menthyl chloroacetate and menthyl acrylate,⁴ and cobalt(0) or nickel(0) complex-catalyzed cyclopropanation of dimethyl fumarate with dibromomethane.⁵ The present method is characterized by good chemical and high optical yields, simple operation, preparation of both enantiomers with equal ease, and the ready availability of the starting materials.

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TABLE

ASYMMETRIC SYNTHESIS OF CYCLOALKANE DICARBOXYLATES



Electrophile		Yield	% Diastereomeric	Configuration
X	n	(%)	Excess	
Br	2	72	~a,b	~c
Br	3	77	65	S,S
OTs	3	63	92	S,S
OTs	3	64	88	R,R ^d
Cl ^e	3	57	83 ^a	~c
OTs	4	61	75	S,S

^aReaction first at -100°C, and then warming to -20°C.

^bNot determined. $[\alpha]_D^{25}$ -51.7° (CHCl₃, c 1.0).

^cNot determined.

^dd-Menthyl ester was used.

^e3-Chloro-2-chloromethyl-1-propene.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(-)-Dimenthyl succinate: Butanedioic acid, bis[5-methyl-2-(1-methylethyl)-cyclohexyl]ester, [1R-[1 α (1R^{*},2S^{*},5R^{*}),2 β ,5 α]]- (9); (34212-59-4)

(-)-Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate: 1,2-Cyclopropanedicarboxylic acid, bis[5-methyl-2-(1-methylethyl)cyclohexyl] ester [1S-[1 (1S^{*},2S^{*},5R^{*}), 2 β ,5 α]]- (11); (96149-01-8)

-(-)-Menthol: Menthol, (-)- (8); Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1 α ,2 β ,5 α)]- (9); (2216-51-5)

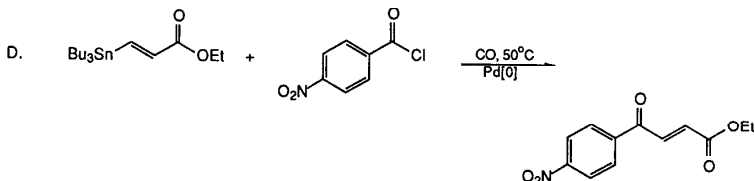
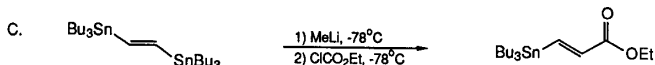
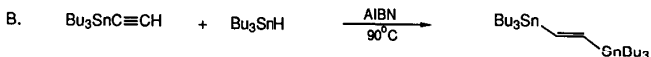
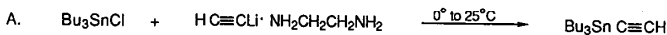
2,2,6,6-Tetramethylpiperidine: Piperidine, 2,2,6,6-tetramethyl- (8,9); (768-66-1)

(+)-(1S,2S)-Cyclopropane-1,2-dicarboxylic acid: 1,2-Cyclopropanedicarboxylic acid, (S,S)-(+)- (8); 1,2-Cyclopropanedicarboxylic acid, (1S-trans)- (9); (14590-54-6)

PALLADIUM-CATALYZED COUPLING OF ACID CHLORIDES WITH ORGANOTIN REAGENTS:

ETHYL (E)-4-(4-NITROPHENYL)-4-OXO-2-BUTENOATE

(2-Butenoic acid, 4-(4-nitrophenyl)-4-oxo-, ethyl ester, (E)-)



Submitted by A. F. Renaldo, J. W. Labadie and J. K. Stille.¹

Checked by Robert Aslanian, Cynthia A. Smith and Andrew S. Kende.

1. Procedure

Caution! Most tin compounds are toxic² and their preparation should be carried out in a well-ventilated hood.

A. *Tributylethynylstannane.* An oven-dried, 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 100-mL addition funnel, and a nitrogen inlet is charged with 24.0 g (0.26 mol) of lithium acetylide, ethylenediamine complex (Note 1). The system is evacuated, placed under nitrogen, and 800 mL of tetrahydrofuran (Note 2) is added to the system via a cannula. The flask is cooled in an ice water bath and 70.7 g (0.22 mol) of tributyltin chloride (Note 3) is added dropwise over 45 min. The ice bath is removed and the mixture is stirred for 18 hr at room temperature. The flask is placed in an ice water bath and excess lithium acetylide is hydrolyzed with 20 mL of water. The reaction mixture is concentrated under reduced pressure and washed with hexane (3 x 50 mL). The organic layers are combined and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent at reduced pressure gives a colorless oil. Distillation yields 21.4-24.3 g (31-35%) of tributylethynylstannane, bp 90-94°C (0.5 mm) as a water-white liquid (Notes 4-6).

B. *(E)-1,2-Bis(tributylstannyl)ethylene.* In a 200-mL, one-necked, round-bottomed flask which contains a magnetic stirring bar and nitrogen inlet are placed 20.6 g (0.066 mol) of tributylethynylstannane, 23.1 g (0.079 mol) of tributyltin hydride (Note 7) and 0.25 g (0.0016 mol) of 2,2'-azobis(2-methylpropionitrile) (Note 8). The mixture is heated at 90°C with stirring for 6 hr. Distillation (170-186°C, 0.3 mm) yields 35.1-36.6 g (88-92%) of (E)-1,2-bis(tributylstannyl)ethylene as a clear colorless oil (Notes 9-10).

C. *Ethyl (E)-3-(tributylstannyl)propenoate*. A flame-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, 100-mL pressure-equalizing addition funnel (Note 11), and a nitrogen inlet is charged with 26.7 g (0.044 mol) of (E)-1,2-bis(tributylstannyl)ethylene. Tetrahydrofuran (100 mL) is added to the flask by cannula. The system is cooled in a dry ice-acetone bath and the addition funnel is charged, under nitrogen, with 44.8 mL of a 1.2 M solution of methylolithium (0.054 mol) in ethyl ether by means of a double-ended needle (Notes 12-13). After 10 min the lithium reagent is added dropwise to the flask over a period of 40 min. After the addition is complete, the yellow solution is stirred for an additional 2 hr at -78°C during which time a 1-L, one-necked, round-bottomed flask, containing a magnetic stirring bar, is flame-dried under nitrogen. The 1-L flask, capped with a rubber septum, is charged with a solution of 5.8 g (0.053 mol) of ethyl chloroformate (Note 14) in 150 mL of tetrahydrofuran and cooled to -78°C with a dry ice-acetone bath. Under gentle nitrogen pressure, the metallated reagent is transferred dropwise over a 2.0-hr period by means of a double-ended needle to the 1-L flask containing ethyl chloroformate while the temperature of both flasks is maintained at -78°C (Note 15). After the addition is complete, the reaction mixture is allowed to stir an additional 30 min at -78°C and then treated with 20 mL of methanol in one portion. After 10 min at -78°C the reaction mixture, while still cold, is transferred to a 1-L separatory funnel containing 200 mL of water and 100 mL of hexane. The organic layer is separated and the aqueous layer is washed with hexane (3 x 50 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered and concentrated to give a dark brown oil. The product is dissolved in hexane (30 mL) and purified by chromatography on a column of silica gel (600 g) (Note 16). Elution is carried out initially with hexane (Note 17) and

then with hexane/ethyl acetate (95:5). Fractions containing the product are combined to give 10.2 g (59%) of ethyl (E)-3-(tributylstannyl)propenoate (Notes 18-20) as a yellow oil.

D. *Ethyl (E)-4-(4-nitrophenyl)-4-oxo-3-butenolate*. A flame-dried, 150-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and equipped with a side-arm is charged with 3.20 g (17.2 mmol) of p-nitrobenzoyl chloride (Note 21), 0.08 g (0.10 mmol) of benzyl(chloro)bis(triphenylphosphine)palladium(II) (Note 22) and 30 mL of chloroform (Note 23). The bright yellow solution is evacuated and refilled with carbon monoxide (3 cycles) utilizing a gas bag (Notes 24-25). After an additional 10 min at room temperature a solution of 8.0 g (20.6 mmol) of ethyl (E)-3-(tributylstannyl)propenoate in 5 mL of chloroform is added to the flask by syringe. The stirring reaction mixture is heated to 50°C for 12 hr while a pressure of 1 atm of carbon monoxide is maintained (Notes 26-27). The reaction is cooled to room temperature and treated with 18 mL of a 1.2 M solution of pyridinium poly(hydrogen fluoride) (Notes 28-30) along with 10 mL of pyridine. The reaction mixture is allowed to stir at room temperature overnight and then transferred to a 250-mL separatory funnel containing 15 mL of water. After addition of 30 mL of chloroform, the organic layer is washed successively with 10% hydrochloric acid (3 x 20 mL), saturated sodium bicarbonate (3 x 20 mL), water (25 mL), and brine (25 mL). The organic layer is dried over anhydrous sodium sulfate, filtered and concentrated to give a dark brown solid. The product is dissolved in chloroform and 15 g of silica gel (Note 16) is added to the solution. Concentration under reduced pressure gives a brown powder of silica coated with product, which is immediately placed on the top of a column of silica gel (50 g) (Note 16). Elution is carried out with ethyl acetate and the fractions are combined and concentrated under reduced pressure (Note

31). The crude product is again placed on a column of silica gel (250 g). Elution is carried out with hexane/ethyl acetate (90:10). Fractions containing the product (obtained by collecting the bright yellow band on the column) are combined to give 3.42 g (80%) of ethyl (E)-4-(4-nitrophenyl)-4-oxo-2-butenolate as yellow-green crystals, mp 69-71°C (Note 32).

2. Notes

1. Lithium acetylide, ethylenediamine complex is purchased from Aldrich Chemical Company, Inc. and used without purification.

2. Tetrahydrofuran is freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.

3. Tributyltin chloride, purchased from Alfa Products, Morton/Thiokol, Inc., is distilled immediately before use (bp 128-130°C, 3 mm).

4. This procedure is a modification of that reported by Seitz.³

5. The remaining fraction of the mixture after distillation was bis-(tributylstannyl)acetylene which could be recycled for the preparation of tributylethynylstannane.

6. The spectral properties are as follows: ¹H NMR (270 MHz, CDCl₃) δ: 0.88 (t, 9 H, J = 7.3), 0.93-1.02 (m, 6 H), 1.25-1.38 (m, 6 H), 1.49-1.60 (m, 6 H), 2.17 (s, 1 H). The infrared spectrum (neat) shows absorption at 3260 and 2000 cm⁻¹.

7. Tributyltin hydride is prepared by the procedure of Hayashi⁴ in 75% yield on a 0.3-mol scale. The checkers used material from Alfa Products, Morton/Thiokol, Inc., which was vacuum distilled before use (bp 75-78°C, 0.7 mm).

8. 2,2'-Azobis(2-methylpropionitrile), purchased from Alfa Products, Morton/Thiokol, Inc., is recrystallized from chloroform prior to use.

9. The submitters report bp 180-218°C (0.5 mm). The spectral properties are as follows: ^1H NMR (270 MHz, CDCl_3) δ : 0.75-1.02 (m, 30 H), 1.21-1.43 (m, 12 H), 1.48-1.63 (m, 12 H), 6.85 (s, 2 H). The infrared spectrum (neat) shows absorption at 1425 and 1020 cm^{-1} .

10. (E)-1,2-Bis(tributystannyl)ethylene has been prepared by an alternative procedure using lithium chloroacetylide.⁵

11. The funnel is capped with a rubber septum. For ease of operation, volume markings, which correspond to the amount of methyllithium to be added, are put on the addition funnel.

12. *Caution! Methyllithium is pyrophoric in air; excess quantities of the reagent should be discarded very carefully.*

13. Methyllithium is purchased from Aldrich Chemical Company, Inc. Although butyllithium could also be used in the metallation step, a cleaner product is obtained with methyllithium.

14. Ethyl chloroformate, purchased from Aldrich Chemical Company, Inc., is distilled at atmospheric pressure prior to use, discarding the first 25 mL.

15. The solution in the flask which contains the ethyl chloroformate is bright yellow and gradually becomes dark-red on the addition of the metallated reagent.

16. The checkers used Kieselgel 60, (230-400 mesh) purchased from E. Merck. The submitters used silica gel (32-63 mesh) purchased from Universal Scientific Inc.

17. Hexane removes the methyltributyltin.

18. The spectral properties are as follows: ^1H NMR (270 MHz, CDCl_3) δ : 0.78-0.99 (m, 12 H), 1.01-1.49 (m, 18 H), 4.11 (q, 2 H, $J = 7.3$), 6.22 (d, 1 H, $J = 19.7$), 7.65 (d, 1 H, $J = 19.6$). The infrared spectrum (neat) shows absorption at 1715, 1580 and 1200 cm^{-1} .

19. Attempts to purify the product by vacuum distillation, bp $110\text{--}138^\circ\text{C}$ (0.05 mm), result in 7-8% isomerization to ethyl (Z)-3-(tributylstannyl)-propenoate [based on ^1H NMR (270 MHz) analysis].

20. The product should be stored under nitrogen at 0°C to prevent decomposition.

21. p-Nitrobenzoyl chloride, purchased from Aldrich Chemical Company, Inc., is recrystallized from hexane prior to use.

22. Benzyl(chloro)bis(triphenylphosphine)palladium(II) is prepared from tetrakis(triphenylphosphine)palladium(0)⁶ (also available from Aldrich Chemical Company, Inc.) by the procedure of Fitton.⁷

23. Chloroform is freshly distilled at atmospheric pressure under nitrogen and filtered through a plug of neutral alumina.

24. The bright yellow color of the solution changes to light green after saturation with carbon monoxide. The presence of carbon monoxide prevents decarbonylation of the acylpalladium complex and thus the formation of ethyl p-nitrocinnamate.

25. The gas bag is purchased from Fisher Scientific.

26. The pressure of 1 atm is maintained by use of the gas bag.

27. The reaction changes color from light green to bright orange.

28. Pyridinium poly(hydrogen fluoride) is purchased from Aldrich Chemical Company, Inc.

29. The solution of pyridinium poly(hydrogen fluoride) in tetrahydrofuran and pyridine is prepared according to the procedure of Trost.⁸ Pyridine is freshly distilled over calcium hydride at atmospheric pressure and stored over 4Å molecular sieves.

30. The orange reaction mixture changes to deep red and the reaction becomes slightly exothermic (50-60°C).

31. The initial filtration with silica gel is necessary to remove most of the tributyltin fluoride.

32. The spectral properties are as follows: ¹H NMR (270 MHz, CDCl₃) δ: 1.34 (t, 3 H, J = 7.2), 4.30 (q, 2 H, J = 7.2), 6.92 (d, 1 H, J = 15.6), 7.85 (d, 1 H, J = 15.6), 8.13 (d, 2 H, J = 8.9), 8.35 (d, 2 H, J = 8.8); ¹³C NMR (68 MHz, CDCl₃) δ: 14.2, 61.7, 124.1, 129.9, 134.3, 135.5, 141.4, 151.0, 165.1, 188.4. The infrared spectrum (Nujol) shows the following absorption cm⁻¹: 1690, 1660, 1590, 1300, 990, 970 and 710.

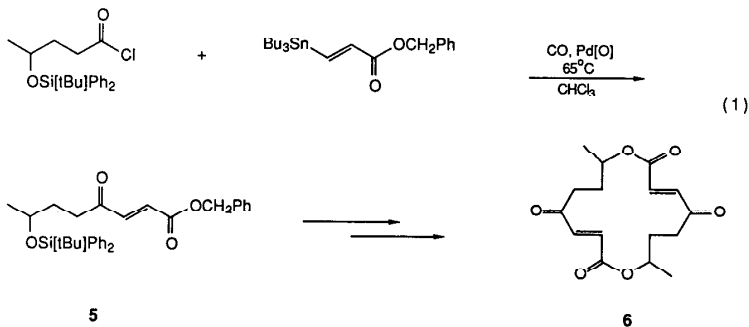
3. Discussion

The procedure for synthesis of the title compound is representative of the palladium-catalyzed coupling of acid chlorides with organotin reagents.⁹ The formation of ketones by Grignard reagents,¹⁰ organocuprates,¹¹ and organoborates¹² has been reported. The principal advantage of the palladium-catalyzed organotin coupling method lies in the broad range of functionality that can be introduced in the product. The reaction can be carried out under mild, neutral conditions with functional groups on the acid chloride such as nitro, nitrile, haloaryl, methoxy, ester and even aldehyde.^{9d} Solvents other than chloroform, such as tetrahydrofuran, hexamethylphosphorictriamide, and dichloromethane can be used in this reaction.

The unsymmetrical tetraorganotin reagent has been demonstrated to transfer selectively the vinyl group rapidly without butyl transfer occurring. By using a tributyl or trimethyl organotin reagent, e.g. Bu_3SnR or Me_3SnR , the order of transfer of the R groups is: $\text{RC}\equiv\text{C}- > \text{RCH}=\text{CH}- > \text{Ar}- > \text{RCH}=\text{CH}-\text{CH}_2- > \text{ArCH}_2- > \text{CH}_3\text{OCH}_2- > \text{C}_n\text{H}_{2n+1}$.¹³

A number of functionalized organotin derivatives have been used in palladium-catalyzed coupling to produce aromatic heterocyclic ketones,¹⁴ acetylenic ketones,¹⁵ and vinyl ketones.¹⁶ The organotin coupling method has been used effectively in the preparation of a key methyl ketone intermediate in the total synthesis of (\pm)-quadron¹⁷ and in the preparation of 5, a key precursor in the synthesis of the antibiotic pyrenophorin 6 (eq. 1).^{13b}

The organotin reagents are very stable since they can withstand distillation as well as chromatography on silica gel. The procedure for



preparation of tributylethynylstannane (1) in Part A is based on one reported by Bottaro, Hanson and Seitz,³ Bis(tributylstannyl)ethylene (2) has been prepared from lithium chloroacetylide⁵ and tributylethynylstannane.¹⁸ Although ethyl (E)-3-(tributylstannyl)propenoate (3) is produced from

transmetallation¹⁹ of 2 or hydrostannation²⁰ of ethyl propiolate. other known procedures to synthesize 3 include conjugate addition of tributylstannylcuprate²¹ to ethyl propiolate, and tributylstannylcopper to β -substituted acrylates.²²

In most cases the trimethyltin reagents are preferred since the by-product, trimethyltin chloride, can easily be removed by water extraction. In the case of the water-insoluble tributyltin chloride it is necessary to add an aqueous solution of potassium fluoride to an ethereal solution of the product thereby forming insoluble tributyltin fluoride, which can be separated by filtration.^{13,23} However, a completely homogeneous and neutral fluoride source, pyridinium hydrofluoride,⁸ is used in this procedure, making the filtration unnecessary and simplifying the subsequent chromatography step.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tributylethynylstannane: Stannane, tributylethynyl- (8,9); (994-89-8)

Lithium acetylide, ethylenediamine complex: Ethylenediamine, compd. with lithium acetylide ($\text{Li}(\text{HC}_2)$) (1:1) (8); 1,2-Ethanediamine, compd. with lithium acetylide ($\text{Li}(\text{C}_2\text{H})$) (1:1) (9); (6867-30-7)

Tributyltin chloride: Stannane, tributylchloro- (8,9); (1461-22-9)

(E)-1,2-Bis(tributylstannyl)ethylene: Stannane, vinylenebis[tributyl-, (E)- (8); Stannane, 1,2-ethenediylbis[dibutyl-, (E)- (9); (14275-61-7)

p-Nitrobenzoyl chloride: Benzoyl chloride, p-nitro- (8); Benzoyl chloride, 4-nitro- (9); (122-04-3)

Benzylchlorobis(triphenylphosphine)palladium(II);

Palladium, benzylchlorobis(triphenylphosphine)-, trans- (8);

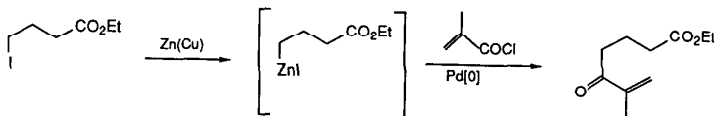
Palladium, chloro(phenylmethyl)bis(triphenylphosphine)-, (SP-4-3)- (9); (22784-59-4)

Tetrakis(triphenylphosphine)palladium(0); Palladium,

tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (142210-01-3)

Pyridinium poly(hydrogen fluoride): Pyridine, compd. with hydrofluoric acid (1:1); Pyridine, hydrofluoride (9); (32001-55-1)

**ETHYL 5-OXO-6-METHYL-6-HEPTENOATE FROM METHACRYLOYL CHLORIDE
AND ETHYL 4-IODOBUTYRATE**



Submitted by Yoshinao Tamaru, Hirofumi Ochiai, Tatsuya Nakamura,
and Zen-ichi Yoshida.¹

Checked by Kevin B. Kunnen and Albert I. Meyers.

1. Procedure

A 300-mL, four-necked, round-bottomed flask containing a magnetic stirring bar is fitted with a serum-cap, thermometer, 100-mL serum-capped pressure-equalizing addition funnel, and a reflux condenser equipped at the top with a nitrogen inlet. The dry apparatus is flushed with nitrogen and 5.6 g (85.5 mmol) of zinc-copper couple (Note 1) and 20 mL of benzene are introduced (Note 2). A mixture of 13.8 g (57 mmol) of ethyl 4-iodobutyrate (Note 3), 9 mL of N,N-dimethylacetamide (Note 4), and 70 mL of benzene is transferred into the addition funnel by cannulation techniques and added to the stirred Zn(Cu) suspension over 3 min at room temperature. The mixture is vigorously stirred for 1 hr at room temperature (Note 5) and then heated at gentle reflux with an oil bath for 4.5 hr (Note 6). After the mixture is cooled to 60°C, a solution of 0.58 g (0.5 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 7) in 15 mL of benzene is added over 1 min

through the addition funnel and stirring is continued for 5 min at the same temperature. The oil bath is removed, a solution of 5.23 g (50 mmol) of methacryloyl chloride (Note 8) in 10 mL of benzene is added through the addition funnel over a period of 5 min, and stirring is continued for 1 hr (Note 9). The mixture is filtered with suction through a Celite pad on a medium-fritted funnel and the filter cake is washed with 200 mL of diethyl ether. The filtrate is washed successively with 50 mL of 1 N ammonium chloride, 10 mL of saturated sodium hydrogen carbonate and 50 mL of saturated sodium chloride. The aqueous phases are extracted with 100 mL of diethyl ether. The combined organic extracts are dried over magnesium sulfate and the solvents are removed with a rotary evaporator to yield a deep brown mobile oil. This is purified by chromatography on 200 g of silica gel with a hexane-diethyl ether gradient (10:1, 400 mL; 5:1, 400 mL, and 2:1, 600 mL) (Note 10), followed by distillation in the presence of hydroquinone (10 mg) in a Kugelrohr apparatus to give 8.0-8.1 g (87-88%) of the product as a colorless liquid, bp 185°C (20 mm) (Note 11).

2. Notes

1. Zinc-copper couple was prepared according to the literature procedure² and kept in a desiccator over phosphorus pentoxide under nitrogen.
2. Benzene is dried by distillation from sodium/benzophenone ketyl.
3. Ethyl 4-iodobutyrate, bp 65°C (2.5 mm), was obtained according to the literature procedure³ (80-90% yield). A mixture of 50 g (0.26 mol) of ethyl 4-bromobutyrate, available from Aldrich Chemical Company, Inc, and 190 g (1.26 mol) of sodium iodide was heated in 500 mL of acetone at 60°C for 24 hr.

4. N,N-Dimethylacetamide (DMA) is dried by distillation under reduced pressure from calcium hydride. The use of DMA is essential to promote metallation.⁴ The metallation is also successful with N,N-dimethylformamide as a co-solvent, but the yield of product is significantly lowered (60-70%) because of formation of acid anhydride.^{4b}

5. The metallation is only slightly exothermic.

6. It is difficult to judge the completion of the metallation by appearance. Although the metallation is reproducible, it is recommended that a reaction aliquot be checked by VPC or TLC after quenching with 1 N hydrochloric acid.

7. Tetrakis(triphenylphosphine)palladium(0) is available from Aldrich Chemical Company, Inc.

8. Methacryloyl chloride, obtained from Aldrich Chemical Company, Inc., is distilled from calcium chloride under nitrogen at atmospheric pressure into a flask containing a small amount of hydroquinone monomethyl ether.

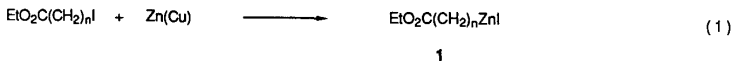
9. The reaction is moderately exothermic and the temperature rises to about 65°C after the addition of methacryloyl chloride and then gradually falls to ambient temperature.

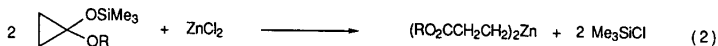
10. The reaction mixture gives only one spot on silica gel TLC (R_f = 0.5, hexane/ethyl acetate = 4:1 using iodine or saturated 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid as an indicator). This column purification is undertaken to help the smooth distillation of the product. Silica gel MERCK in a 5.5-cm diameter column was used.

11. The submitters report bp 100°C (6 mm). The product shows the correct elemental analysis and has the following physical and spectral properties: n_D^{20} 1.4512; IR (liquid film) cm^{-1} : 3100 (w), 2970 (m), 1730 (s), 1680 (s), 1630 (m), 940 (m); ^1H NMR (CDCl_3) δ : 1.25 (t, 3 H, $J = 7.1$), 1.75-2.11 (m, 5 H), 2.35 (t, 2 H, $J = 6.8$), 2.76 (t, 2 H, $J = 7.1$), 4.13 (q, 2 H, $J = 7.1$), 5.77 (br, s, 1 H), 5.96 (s, 1 H); ^{13}C NMR (CDCl_3) δ : 13.9, 17.2, 19.3, 33.0, 36.0, 59.9, 124.1, 144.1, 172.7, 200.6; VPC analysis: 20% Silicone DC550 on Celite (Nishio Kogyo Co.), 3 mm x 1 m column, constant temperature increase 8°C/min from 100°C, one peak of impurity (retention time 1.8 min) and the peak of the product (retention time 9.0 min, 99.5% purity).

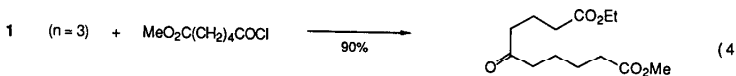
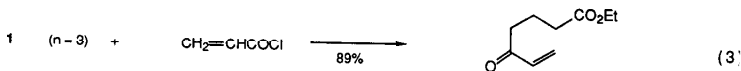
3. Discussion

α -Metallocarbonyl compounds, so called "enolates", are among the most widely used reagents for organic syntheses. Undoubtedly, β -, γ -, and δ -metallocarbonyl compounds are also of great synthetic value. The use of these organometallics, however, has been limited mainly because of the lack of a convenient preparative method. Herein are described the preparation of a γ -metallo ester, 3-carboethoxypropylzinc iodide (**1**, $n = 3$; eq 1), and its reaction with acid chlorides to yield δ -keto esters. According to the same procedure, it is possible to generate 2-carboethoxyethylzinc iodide (**1**, $n = 2$) and 4-carboethoxybutylzinc iodide (**1**, $n = 4$)⁵ with similar efficiency. 2-Carboalkoxyethylzinc may be prepared by a cyclopropane ring-opening procedure (eq 2).⁶

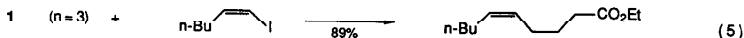




These organozincs, **1** ($n = 2, 3$, and 4), react with diverse acid chlorides to yield γ , δ , and ϵ -keto esters, respectively, in good yields. Two typical examples are shown in eq 3 and 4. The product of eq 3, ethyl 5-oxo-6-heptenoate, may be prepared by laborious, multi-step methods.⁷ The title compound, ethyl 5-oxo-6-methyl-6-heptenoate, is a new compound.



Another use of **1** ($n = 3$) is the coupling with vinyl iodides or triflates, which furnish δ,ϵ -unsaturated esters.⁸ One example is shown in eq 5. The reaction proceeds with retention of the double bond geometry.



1. Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Zinc-copper couple: Copper, compd. with zinc (1:1) (8,9); (12019-27-1)

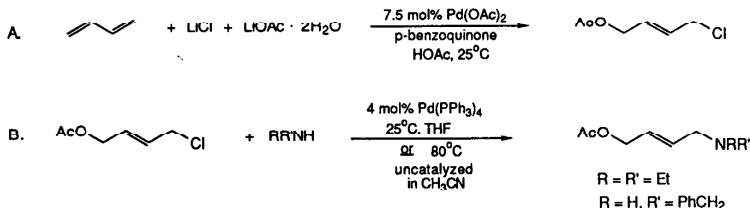
Ethyl 4-iodobutyrate: Butyric acid, 4-iodo-, ethyl ester (8); Butanoic acid, 4-iodo-, ethyl ester (9); (7425-53-8)

Ethyl 4-bromobutyrate: Butyric acid, 4-bromo-, ethyl ester (8); Butanoic acid, 4-bromo-, ethyl ester (9); (2969-81-5)

N,N-Dimethylacetamide: Acetamide, N,N-dimethyl- (8,9); (127-19-5)

Tetrakis(triphenylphosphine)palladium(0): Palladium,
tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-,
(1-4)- (9); (14221-01-3)
Methacryloyl chloride (8); 2-Propenoyl chloride, 2-methyl- (9); (920-46-7)
Hydroquinone (8); 1,4-Benzenediol (9); (123-31-9)

**1,4-FUNCTIONALIZATION OF 1,3-DIENES VIA PALLADIUM-CATALYZED
CHLOROACETOXYLATION AND ALLYLIC AMINATION: 1-ACETOXY-4-DIETHYLAMINO-2-BUTENE
AND 1-ACETOXY-4-BENZYLAMINO-2-BUTENE
(2-Buten-1-ol, 4-(diethylamino)-, acetate (ester))**



Submitted by J. E. Nyström, T. Rein, and J. E. Bäckvall.¹

Checked by Marvin M. Hansen and Clayton H. Heathcock.

1. Procedure

A. 1-Acetoxy-4-chloro-2-butene. In a 2-L, two-necked, round-bottomed flask equipped with a 5-cm egg-shaped magnetic stirring bar and a pressure-reducing outlet (Note 1) is placed 800 mL of pentane (Note 2). The flask is cooled with an ice bath and 5.4 g (0.1 mol) of butadiene is dissolved with stirring (0–5°C) by addition through one of the inlets from a Fluka low pressure bottle of butadiene (Note 3). The pressure-reducing outlet is removed and a freshly prepared solution of 1.68 g (7.5 mmol) of palladium acetate, Pd(OAc)₂, 8.4 g (0.2 mol) of lithium chloride, 20.4 g (0.2 mol) of lithium acetate dihydrate (LiOAc · 2H₂O), and 21.6 g (0.2 mol) of p-benzoquinone in 400 mL of acetic acid is added (Note 4). The cooling bath is removed and

the two-phase system is stirred at a moderate rate (Note 5) at 25°C for 26 hr. A saturated sodium chloride solution (300 mL) is added and after the mixture is stirred for 5 min, it is filtered using a Büchner funnel with an intermediate paper filter using aspirator vacuum. The organic phase is separated and the aqueous phase is extracted with three 300-mL portions of pentane-ether (80:20). The combined organic phases are washed with two 75-mL portions of water, two 100-mL portions of saturated potassium carbonate solution, three 100-mL portions of 2M sodium hydroxide solution, and finally with 50 mL of saturated sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered and concentrated to a volume of 20-30 mL by distilling off the solvent at atmospheric pressure. The remaining solvent is removed with a rotary evaporator at aspirator vacuum to give 13-15 g of crude product, which is distilled (10 mm, 70-90°C) to yield 9.7-12.0 g (65-81%) of a light yellow liquid consisting of 91% of 1-acetoxy-4-chloro-2-butene (E/Z = 90/10) and 9% of 4-acetoxy-3-chloro-1-butene. The chloroacetate is contaminated with approximately 1% of 5,8-dihydronaphthoquinone (Note 6).

Further purification is achieved by the following procedure: The chloroacetate from above is dissolved in 150 mL of ether. This solution is stirred together with a 10-mL aqueous solution saturated with sodium borohydride. The stirring is continued until the yellow color of the organic phase disappears (ca. 15 min). The organic phase is separated and washed with 5 mL of 2M sodium hydroxide solution, 5 mL of a saturated sodium chloride solution, dried over magnesium sulfate and concentrated by distilling off the solvent at atmospheric pressure. The solvent which remains is removed with a rotary evaporator to afford 9.5-10.5 g (64-70%) of chloroacetate, with the same composition as above, but which is now completely free from 5,8-dihydronaphthoquinone (Note 7).

B1. *1-Acetoxy-4-diethylamino-2-butene. Method 1.* In a 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-vacuum inlet, and a rubber septum, is placed 2.77 g (2.4 mmol) of tetrakis(triphenylphosphine)palladium, $\text{Pd(PPh}_3)_4$ (Note 8). The flask is closed, evacuated and filled with nitrogen. This flushing procedure is repeated twice (Note 9). A solution of 8.91 g (0.06 mol) of the chloroacetate from procedure A in 180 mL of dry tetrahydrofuran (Note 10) is added through the membrane with the aid of a 50-mL syringe. With the same syringe 21.9 g (0.30 mol) of diethylamine (Note 11) in 120 mL of dry tetrahydrofuran is added. The mixture is stirred at ambient temperature and the reaction is followed by gas chromatography. When the starting material has been consumed, which takes approximately 4 hr (Note 12), 600 mL of ice-cooled ether and 600 mL of ice-cooled saturated aqueous sodium carbonate solution are added and the mixture is shaken in a separatory funnel (Note 13). The aqueous phase is extracted with ether (2 x 300 mL).

The combined organic phases are washed with 50 mL of saturated potassium carbonate solution, and dried over solid potassium carbonate. Evaporation with a rotary evaporator affords 13.7 g of crude product. The residue is put on a column (silica, 3 x 10 cm) and eluted with 600 mL of ether-pentane-triethylamine (47.5:47.5:5) (Note 14). The main fractions are collected to give 8.15 g (73%) of essentially pure E-1-acetoxy-4-diethylamino-2-butene (>94% E). No 1,2-isomer could be detected. The product is further purified by Kugelrohr distillation to afford 7.81-8.21 g (70-74%) (Note 15).

B2. *1-Acetoxy-4-benzylamino-2-butene. Method 2.* In a 250-mL, one-necked, round-bottomed flask are placed in order 8.91 g (0.06 mol) of the chloroacetate from method A, 100 mL of acetonitrile and 19.3 g (0.18 mol) of benzylamine (Note 6). The flask is equipped with a reflux condenser and the

solution is refluxed for 2 hr using an oil bath at 100-110°C. The reaction mixture is cooled and 150 mL of ether and 100 mL of a saturated sodium carbonate solution are added. The mixture is shaken in a separatory funnel and the organic phase is collected. The aqueous phase is extracted with 50 mL of ether. The combined organic phases are dried over potassium carbonate. The solvent and excess benzylamine are removed by rotary evaporation and Kugelrohr distillation at 50°C (1 mm). Kugelrohr distillation of the crude product gives 9.1-9.9 g (70-76%) of 1-acetoxy-4-benzylamino-2-butene as a 90:10 mixture of the E and Z isomers (Note 17).

2. Notes

1. The pressure-reducing outlet can be a U-shaped tube filled with oil or a thick-walled rubber balloon.
2. Light petroleum, boiling point 40°C, can also be used.
3. The amount of butadiene added is determined by weighing the Fluka bottle and double checked by weighing the reaction flask before and after addition. The checkers purchased butadiene from Matheson and measured it by condensation into a 25-mL flask cooled to -10°C. The cooled material was then transferred by cannula into the reaction vessel containing the pentane, cooled to 0-5°C.
4. p-Benzoquinone, 200 mol%, is needed for a rapid and efficient reaction.
5. A stirring rate of approximately 5 rps is used. The reaction tolerates a variation between 3-10 rps, which gives essentially the same result.

6. 5,8-Dihydronaphthoquinone is the oxidized Diels-Alder adduct between butadiene and benzoquinone.

7. The spectral properties are as follows: ^1H NMR (CDCl_3 , 250 MHz) δ : 2.09 (s, 3 H), 4.06 (m, 2 H), 4.59 (m, 2 H), 5.90 (m, 2 H).

8. Tetrakis(triphenylphosphine)palladium, $\text{Pd}(\text{PPh}_3)_4$, is commercially available but is readily prepared according to ref 2 (or ref 3b). Palladium acetylacetonate, $\text{Pd}(\text{acac})_2$, together with 4 PPh_3 can be used in place of $\text{Pd}(\text{PPh}_3)_4$ and gives essentially the same result.

9. A manifold system connected to a vacuum line and a nitrogen line is used.

10. Tetrahydrofuran is distilled under nitrogen from potassium benzo-phenone.

11. Commercial diethylamine (BDH) is used without further purification.

12. The rate of the reaction varies slightly depending on the quality of the catalyst.

13. The solution is kept cold to avoid hydrolysis of the acetoxy group.

14. The checkers observed that, upon placing the crude product on the top of the silica gel column, the residual $\text{Pd}(\text{PPh}_3)_4$ precipitates. However, the presence of this solid residue does not interfere with the progress of the chromatography or affect the yield of product.

15. The spectral properties are as follows: ^1H NMR (CDCl_3 , 250 MHz) δ : 1.03 (t, 6 H, $J = 7.2$), 2.07 (s, 3 H), 2.51 (q, 4 H, $J = 7.2$), 3.10 (br d, 2 H), 4.55 (br d, 2 H), 5.64-5.90 (m, 2 H).

16. Benzylamine (Fluka) is dried over NaOH and distilled over sodium. The threefold excess of benzylamine is used to depress the dialkylation product.

17. The spectral properties are as follows: ^1H NMR (CDCl_3 , 250 MHz) δ : 1.20-1.60 (br s, 1 H), 2.06 (s, 3 H), 3.28 (br d, 2 H, $J = 5.7$), 3.78 (s, 2 H), 4.55 (br d, 2 H, $J = 5.8$), 5.74 (dt, 1 H, $J = 15.5, 5.8$), 5.88 (dt, 1 H, $J = 15.7, 5.7$), 7.20-7.45 (m, 5 H).

3. Discussion

The procedure reported here provides an efficient method for the preparation of 4-amino-2-alken-1-ol derivatives. It is based on the palladium-catalyzed 1,4-acetoxychlorination of 1,3-dienes³ and palladium-catalyzed amination of allylic substrates.⁴ Compared to other methods⁵ this method is more convenient and more general. It allows complete control of the 1,4-relative configuration when the carbons bearing nitrogen and oxygen are stereogenic. In these cases the chloride is replaced with *retention* according to procedure B1 but with *inversion* according to procedure B2.^{3b,6}

Procedure A is very effective for a range of acyclic and cyclic conjugated dienes.³ The major side reaction in the chloroacetoxylation is Diels-Alder addition of p-benzoquinone to the diene. The purpose of the pentane phase is to ensure a low concentration of diene in the acetic acid phase, which depresses the Diels-Alder reaction. The reaction can also be performed without the pentane phase with slow addition of the diene using a syringe pump.

Some representative examples of the amination reaction according to procedure B are shown in Table I.

1. Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden.
2. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
3. (a) Räckvall, J. E.; Nordberg, R. E.; Nyström, J. E. *Tetrahedron Lett.* **1982**, *23*, 1617; (b) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
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6. Backvall, J. E. *Pure Appl. Chem.* **1983**, *55*, 1669.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 1-Acetoxy-4-diethylamino-2-butene: 2-Buten-1-ol, 4-(diethylamino)-, acetate (ester) (11); (82736-47-8)
- 1-Acetoxy-4-chloro-2-butene: 2-Buten-1-ol, 4-chloro-, acetate (E)- (9); (34414-28-3)
- Palladium acetate: Acetic acid, palladium(2+) salt (8,9); (3375-31-3)
- Lithium acetate dihydrate: Acetic acid, lithium salt, dihydrate (8,9); (6108-17-4)

4-Acetoxy-3-chloro-1-butene: 3-Buten-1-ol, 2-chloro-, acetate (11);
(96039-67-7)

Tetrakis(triphenylphosphine)palladium:

Palladium, tetrakis(triphenylphosphine)- (8);

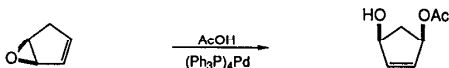
Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

TABLE

Chloroacetate ^a	Amine	Procedure	Aminoacetate	Yield(%)
	Et ₂ NH	B1		87 ^b
		B2		75
	EtNH ₂	B2		89
	Me ₂ NH	B2		76
	PhCH ₂ NH ₂	B2		89
	Et ₂ NH	B1		80
		B2		70
	Me ₂ NH	B1		95
		B2		93
	MeNH ₂	B1		87

a) The chloroacetates were prepared from the corresponding dienes according to procedure A or the modified version without the pentane phase (see discussion). b) From a small scale experiment with acid extraction in the work-up. c) E/Z = 3.5/1. d) >94% R*R*. e) >90% R*S*. f) >98% cis. g) >98% trans. h) >95% β,β,α.

**PALLADIUM(0)-CATALYZED syn-1,4-ADDITION OF CARBOXYLIC ACIDS
TO CYCLOPENTADIENE MONOEPoxide: cis-3-ACETOXY-5-HYDROXYCYCLOPENT-1-ENE
(4-Cyclopentene-1,3-diol, monoacetate, cis-)**



Submitted by Donald R. Deardorff and David C. Myles.¹

Checked by Helmut Grebe and Ekkehard Winterfeldt.

1. Procedure

An oven-dried, 300-mL, two-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar, pressure equalizing dropping funnel, and a rubber septum with an 18-gauge needle connected to a dry nitrogen source. The nitrogen-flushed apparatus is charged with 125 mL of dry tetrahydrofuran (Note 1) and 0.28 g (0.24 mmol, 0.2 mol%) of tetrakis(tri-phenylphosphine)palladium(0) (Note 2). The mixture is stirred at room temperature until all of the palladium catalyst dissolves (Note 3). The solution is cooled in an ice-water bath and 7.0 mL (7.3 g, 122 mmol) of acetic acid (Note 4) is added via syringe. At this point a slight darkening of the solution is observed. A room temperature solution containing 10.9 g of 92% cyclopentadiene monoepoxide (10.0 g, 122 mmol, Note 5) in 40 mL of tetrahydrofuran is added over 10 min with the aid of the addition funnel. The original pale yellow color gives way to a deeper transparent orange. After 5 min (Note 6), the solution is concentrated at ambient temperature under

reduced pressure and the resulting reddish-brown oil is passed through a plug of silica gel (50 g, Note 7) with 450 mL of ethyl ether (Note 8). The slightly cloudy filtrate is washed through a plug of anhydrous magnesium sulfate (60 g, 5 x 7 cm coarse glass frit) with an additional 150 mL of ether (Note 9). The solvent is removed under reduced pressure to yield a pale yellow oil. The material is distilled through a short path apparatus at 73-75°C (0.15 mm) to afford 12.5-13.2 g (72-76%) of colorless oil which crystallizes upon refrigeration (mp 36-39°C). The material is homogeneous by TLC and ^1H NMR (Note 10), but can be further purified by recrystallization from an ether-hexane mixture to give colorless crystals, mp 38.5-41°C, (Note 11).

2. Notes

1. Tetrahydrofuran was predried over potassium hydroxide, then dried by distillation from sodium/benzophenone ketyl under nitrogen.

2. Tetrakis(triphenylphosphine)palladium(0) was purchased from Aldrich Chemical Company, Inc., and used without further purification. No special precautions were taken in handling the catalyst.

3. Dissolution takes approximately 2-3 min.

4. Glacial acetic acid was purchased from J. T. Baker Chemical Company (Baker Analyzed Reagent) and distilled prior to use.

5. Cyclopentadiene monoepoxide was prepared from cyclopentadiene and peracetic acid according to the well-established procedure of Korach et al.² However, the submitters report that epoxidation of cyclopentadiene under conditions developed by Knapp et al.³ for cyclohexadiene increased their isolated yields from 40% to 62%. The major impurity in distilled

cyclopentadiene monoepoxide is 3-cyclopentenone. This by-product can be conveniently assayed by ^1H NMR integration of the four methylene protons which appear as a broad singlet at 2.80 δ . Epoxide purity can be determined by GLC analysis on a 25 M Carbowax capillary column operated at 50°C.

6. TLC analysis using Baker Si250F precoated glass plates with a hexane-ethyl acetate (1:1) solvent system indicates that all of the starting material is consumed.

7. Baker Analyzed Reagent silica gel 60-200 mesh was used in a 4.5 x 9.0-cm column. This step removes most palladium-containing compounds from the reaction mixture. In order to insure that the palladium is efficiently separated, it is important that all tetrahydrofuran be removed from the crude oil prior to filtration.

8. Anhydrous ether (purified) was purchased from J. T. Baker Chemical Company and used without additional purification.

9. This step removes the final traces of palladium. It is imperative that all catalyst be removed prior to distillation since upon heating this metal catalyzes the decomposition of cis-3-acetoxy-5-hydroxycyclopent-1-ene into isomeric cyclopentenones and acetic acid.

10. cis-3-Acetoxy-5-hydroxycyclopent-1-ene has the following spectral characteristics: ^1H NMR (200 MHz, CDCl_3) δ : 1.59 (dt, 1 H, $J = 4.0$ and 14.5, CH_2), 2.00 (s, 3 H, CH_3), 2.38 (br s, 1 H, OH), 2.76 (quintet, overlapping dt, 1 H, $J = 7.4$ and 14.5, CH_2), 4.67 (m, 1 H, CHOH), 5.45 (m, 1 H, CHOAc), 5.92 (m, 1 H, $\text{CH}=\text{CH}$), 6.05 (m, 1 H, $\text{CH}=\text{CH}$); IR (neat) cm^{-1} : 3410 (s), 1720 (s), 1250 (s).

11. 4-Acetoxy-2-cyclopentenone could be prepared in 85% yield by treatment of 1 equiv of this alcohol with 1.1 equiv of pyridinium chlorochromate in methylene chloride for 1 hr at room temperature, followed by washing with water, concentration, and distillation.

3. Discussion

Functionalized cyclopentenoids have been used extensively as key building blocks for the synthesis of many biologically active molecules.⁴ This procedure details the facile preparation of one such versatile intermediate: *cis*-3-acetoxy-5-hydroxycyclopent-1-ene. Although important in its own right, this material also serves as a one-step precursor to the highly useful synthetic substrate 4-acetoxy-2-cyclopenten-1-one.⁴ Only the acetic acid adduct with cyclopentadiene monoepoxide is described here. However, this palladium-catalyzed reaction appears general for other acidic substrates as well.^{5,6} For example, the corresponding benzoate and phenyl ether adducts have been successfully prepared⁵ from both benzoic acid and phenol in yields of 87% and 82%, respectively. Moreover, the reaction is not limited to just the monoprotected versions of *cis*-cyclopentene-3,5-diol. The corresponding diesters can be similarly prepared by replacement of the carboxylic acid component with an anhydride. This minor modification permits direct synthetic access to either the dibenzoate or diacetate in equally good yields (74% and 79% respectively). Recently, silyl carboxylates and silyl phenoxides were also found to react analogously with cyclopentadiene monoepoxide in the presence of Pd(0) catalyst.⁷ It should be stressed that in each case only the *cis*-1,4-adducts are observed, despite the fact that three other stereoisomers are possible. This remarkable stereo- and regiospecificity is undoubtedly a manifestation of an intermediate palladium π -allyl complex.⁸

Racemic cis-monoesters of cyclopentene-3,5-diol have been previously prepared by the selective acylation⁹ of the meso-diol and the copper-mediated¹⁰ addition of carboxylic acid salts to cyclopentadiene monoepoxide. Optically active monoacetates can be accessed by enzymatic hydrolysis¹¹ of the corresponding diester. The present method offers four principal advantages over the earlier reports: (1) it is operationally simple, (2) it requires a much shorter reaction time, (3) it gives better yields, and (4) it has widespread applicability, since reactants other than carboxylic acids may be employed with equally good results.

A major disadvantage with the acylation method⁹ is that the starting material, cis-cyclopentene-3,5-diol, is not readily available and must be prepared via photooxygenation procedures.¹² Furthermore, acylation occurs with the concomitant formation of diacylated product which results in reduced yields and associated purification problems. The copper-mediated¹⁰ and palladium-catalyzed procedures share some similarities in that they both use cyclopentadiene monoepoxide as their starting material and deliver the desired product in good yield. But, unlike the palladium-catalyzed method, copper-mediated reactions require two full equivalents of carboxylate salt, much lower reaction temperatures (-78°C), and substantially longer reaction times. Finally, the enantioselective hydrolysis¹¹ of cis-3,5-diacetoxycyclopent-1-ene by hydrolase enzymes is an effective two-step method for generating optically-enriched product.

1. Department of Chemistry, Occidental College, Los Angeles, CA 90041. This work was supported by a Penta Corporation Grant of Research Corporation.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclopentadiene monoepoxide: 6-Oxabicyclo[3.1.0]hex-2-ene (8,9);
(7129-41-1)

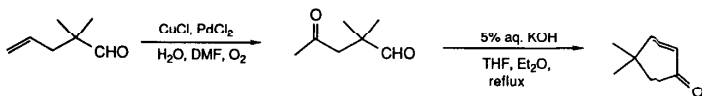
cis-3-Acetoxy-5-hydroxycyclopent-1-ene: 4-Cyclopenten-1,3-diol, monoacetate,
cis- (9); (60410-18-6)

Tetrakis(triphenylphosphine)palladium(0):

Palladium, tetrakis(triphenylphosphine)- (8);

Palladium, tetrakis(triphenylphosphine)-, (I-4)- (9); (14221-01-3)

4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE
(2-Cyclopenten-1-one, 4,4-dimethyl-)



Submitted by David Pauley, Frank Anderson, and Tomas Hudlicky.¹

Checked by David M. Fink and Andrew S. Kende.

1. Procedure

A. *2,2-Dimethyl-4-oxopentanal* (Note 1). Oxygen is bubbled for 2 hr through a stirred solution of copper(I) chloride (32.8 g, 0.33 mol), palladium(II) chloride (1.19 g, 0.007 mol), 329 mL of dimethylformamide, and 331 mL of water in a 2-L, three-necked, round-bottomed flask cooled in a water bath. 2,2-Dimethyl-4-pentenal (185.6 g, 1.66 mol) (Note 2) is added to the solution and oxygen is bubbled through for an additional 60 hr at room temperature. The solution is acidified to litmus with 10% hydrochloric acid and extracted four times with 200 mL of ethyl ether. The combined organic layers are washed three times with 200 mL of saturated sodium chloride solution and dried over sodium sulfate. The ether is removed first by rotary evaporation and then under reduced pressure (0.2 mm). In this way 133.6 g (1.04 mol) of keto-aldehyde is obtained in 62.7% yield. The original aqueous layer is saturated with sodium chloride and extracted five times with 200 mL of anhydrous ethyl ether. The combined organic layers are washed three times with 200 mL of saturated sodium chloride solution and dried over sodium

sulfate. Solvent is removed by rotary evaporation and vacuum pump. An additional 31.5 g (0.25 mol) of keto-aldehyde is recovered to give a total yield of 78% (Note 3); bp 32°C (0.3 mm) (Note 4).

B. *1,4-Dimethyl-3-cyclopenten-1-one*. A 3-L, round-bottomed flask, containing a solution of 600 mL of aqueous 5% potassium hydroxide, 300 mL of tetrahydrofuran, 1350 mL of ethyl ether, and 165.1 g (1.29 mol) 2,2-dimethyl-4-oxopentanal, is equipped with a mechanical stirrer and reflux condenser. The solution is heated under reflux for 66 hr under a nitrogen atmosphere. Upon completion, the organic layer is washed three times with 200 mL of saturated sodium chloride solution and dried over sodium sulfate. The aqueous layer is extracted three times with 200 mL of anhydrous ethyl ether. The resulting organic layers are washed three times with saturated sodium chloride solution and dried over sodium sulfate. All organic layers are evaporated using aspirator vacuum and a rotary evaporator and combined. The residual ether is removed under reduced pressure to yield 89.7 g (63%) of 4,4-dimethyl-2-cyclopenten-1-one. bp 32°C (0.3 mm) (Notes 5-7).

2. Notes

1. This procedure was originally described by Magnus.²
2. 2,2-Dimethyl-4-pentenal was prepared as described in *Org. Synth.* 1984, 62, 125.
3. The product is sufficiently pure to be used in the next reaction without purification.
4. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 2990, 2730, 1740, 1485, 1380; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.12 (s, 6 H), 2.14 (s, 3 H), 2.7 (s, 2 H), 9.52 (s, 1 H).

5. This product is volatile. The checkers found one-third of the product in a vacuum trap after 24 hr at ca. 5 mm.

6. The checkers distilled the product (Kugelrohr 8 mm, 80°C) and obtained yields of 83% (one-third scale) and 79% (two-thirds scale).

7. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 2970, 2890, 1730, 1600, 1480, 1430; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.20 (s, 6 H), 2.21 (s, 2 H), 5.97 (d, 1 H, $J = 6$), 7.46 (d, 1 H, $J = 6$).

3. DISCUSSION

4,4-Dimethyl-2-cyclopenten-1-one is a valuable starting material in terpenoid synthesis and in cases where a gem-dimethylcyclopentane unit needs to be introduced. It is useful as a starting material in further functionalization. Its preparation by the method of Magnus² is amenable to large scale synthesis.

Acknowledgment

The authors thank Professor P. D. Magnus for permission to use his method for the scale up reported here.

1. Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061.
2. Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* 1980, 10, 273.

Appendix

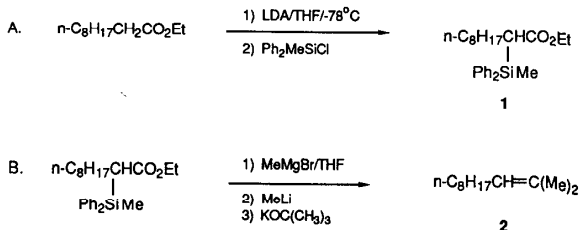
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 4,4-Dimethyl-2-cyclopenten-1-one: 2-Cyclopenten-1-one, 4,4-dimethyl- (8,9);
(22748-16-9)
- 2,2-Dimethyl-4-oxopentanal: Pentanal, 2,2-dimethyl-4-oxo- (9); (61031-76-3)

α -DIPHENYLMETHYLSILYLATION OF ESTER ENOLATES:

2-METHYL-2-UNDECENE FROM ETHYL DECANOATE

(2-Undecene, 2-methyl-)



Submitted by Gerald L. Larson, Ingrid Montes de Lopez-Copero, and Luis Rodriguez Miele.¹

Checked by Choon Sup Ra and Leo A. Paquette.

1. Procedure

A. *Ethyl 2-(diphenylmethylsilyl)decanoate*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, 100-mL pressure-equalizing dropping funnel and a no-air stopper is flame-dried under a vigorous flow of nitrogen, cooled under an atmosphere of nitrogen to -78°C with a dry ice-acetone bath and charged with 39.2 mL (52.5 mmol) of a 1.34 M solution of butyllithium in hexane (Note 1). To this solution is added 7.4 mL (5.31 g; 52.5 mmol) of diisopropylamine (Note 2) in 7 mL of tetrahydrofuran (Note 3). The resulting solution is warmed to ambient temperature and held for 30 min. The solution is diluted with 50 mL of dry tetrahydrofuran and

cooled again to -78°C . To this solution is added 11.6 mL (10.0 g; 50 mmol) of ethyl decanoate (Note 4) in 45 mL of tetrahydrofuran dropwise over a 30-min period. The mixture is kept at -78°C for 30 min to allow the enolate to form, and then 10.3 mL (11.6 g; 50 mmol) of diphenylmethylchlorosilane (Note 5) in 40 mL of tetrahydrofuran is added over a 5-min period. The reaction mixture is allowed to reach ambient temperature and stir at that temperature for 8 hr. It then is cooled to 0°C , diluted with hexane (150 mL), washed with cold water (2 x 100 mL), dried over magnesium sulfate, filtered and concentrated at reduced pressure (Note 6). The crude product, which is ca. 95% pure (Note 7), is purified by rapid filtration through 50 g of silica gel (Note 8) with 1% ethyl acetate-hexane (Note 9) as eluant. There is obtained 18.4-18.7 g (93-94%) of ethyl 2-(diphenylmethylsilyl)decanoate (Note 10). Similar results are obtained on a larger scale (Note 11).

B. 2-Methyl-2-undecene. A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, 500-mL pressure-equalizing dropping funnel and no-air stopper is flame-dried under vacuum, cooled to room temperature under an atmosphere of nitrogen and charged with 87 mL (260 mmol) of 3 M methylmagnesium bromide in ether (Note 12). This solution is cooled to 0°C (ice bath) and 52 g (130 mmol) of ethyl 2-(diphenylmethylsilyl)decanoate in 260 mL of tetrahydrofuran (Note 3) is added over an 8-min period. After the addition is complete, the reaction mixture is warmed to room temperature and heated to reflux for 24 hr. The reaction mixture is again cooled to 0°C and 244 mL (390 mmol) of 1.6 M methylolithium in tetrahydrofuran (Note 13) is added over a period of 30 min. After the addition is complete, the reaction mixture is heated to reflux for 24 hr, cooled to 0°C (ice bath) and 29.2 g (260 mmol) of solid potassium tert-butoxide (Note 14) is added in three portions (Note 15). The reaction mixture is heated to reflux for 1 hr, cooled

to 0°C, diluted with hexane (100 mL) and hydrolyzed by the dropwise addition of 1 M hydrochloric acid (240 mL), followed by about 150 mL of 3 M hydrochloric acid until a pH of 4 is reached (Note 16). The organic layer is separated and the aqueous layer is extracted with hexane (3 x 100 mL). The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (Note 6) to give 55 g of crude material (Note 17). This material is diluted with 150 mL of dry hexane (Note 18) and applied to a silica gel column (Note 8). The product is obtained by eluting with hexane and collecting 200-mL fractions. This material, which contains small amounts of dimethyldiphenylsilane and diphenylmethylsilanol, is chromatographed under 3-5 psi on a silica gel column (50 x 2.8 cm) eluting with hexane (Note 19) to give 11.3 g (51.8%) of the olefin (Note 20).

2. Notes

1. Butyllithium was purchased from Foote Mineral Company and titrated by the method of Watson and Eastman.²

2. Diisopropylamine was purchased from Aldrich Chemical Company, Inc., and distilled from calcium hydride prior to use.

3. Tetrahydrofuran was a gift from Pfizer Pharmaceuticals of Puerto Rico purchased by them from Dupont Company. It was distilled from sodium/benzophenone prior to use.

4. Ethyl decanoate was purchased from Aldrich Chemical Company, Inc., and used without further purification.

5. Diphenylmethylchlorosilane was purchased from Petrarch Systems, Inc., and distilled from calcium hydride (bp 85°C/0.1 mm) prior to use. A 187.5-mmol scale reaction using diphenylmethylchlorosilane purchased from Petrarch Systems and used without purification gave an 89% yield of the α -silyl ester.

6. A high volume house vacuum system was used for this step.

7. The minor impurities are unreacted ethyl decanoate and diphenyl-methylsilanol.

8. Chromatographic silica gel, 70-230 mesh, from Matheson-Coleman-Bell was used.

9. Alternatively, the product can be distilled in an Aldrich Kugelrohr apparatus (pot temperature 130-135°C at 0.2 mm) to give slightly lower (80-90%) yields.

10. The physical properties are as follows: n_D^{20} 1.5190; IR (neat) cm^{-1} : 3068, 3045, 2950-2850, 1714, 1589, 1254, 790; ^1H NMR (CDCl_3 , 80 MHz) δ : 0.66 (s, 3 H), 0.95 (t, 3 H, $J = 1$), 1.21 (brs, 14 H), 2.56 (m, 1 H), 3.86 (m, 2 H), 7.29-7.62 (m, 10 H); ^{13}C NMR (CDCl_3) δ : 3.39, -5.57, 14.01, 22.63, 25.02, 27.56, 29.20, 29.35, 30.51, 31.87, 36.39, 59.75, 127.71, 129.50, 129.56, 134.32, 134.64, 134.78, 134.83, 175.02; MS 70 eV m/e (rel. abundance) 398 (10), 397 (19), 396 (33), 353 (21), 351 (20), 319 (27), 298 (39), 297 (75), 284 (23), 227 (33), 199 (30), 198 (43), 197 (100), 195 (30), 183 (26), 181 (27), 121 (35), 105 (39), 93 (20), 73 (24), 69 (21), 55 (36), 53 (16). Anal. Calcd. for $\text{C}_{25}\text{H}_{36}\text{O}_2\text{Si}$: C, 75.76, H, 9.09. Found: C, 75.59, H, 9.19.

11. The submitters report that a 187.5-mmol scale reaction gave an 89% yield of product.

12. Methylmagnesium bromide was purchased from Columbia Organic Chemicals as a 3 M solution and used as obtained.

13. Methylolithium was purchased from Aldrich Chemical Company, Inc., and titrated prior to use.²

14. Potassium tert-butoxide was purchased from Aldrich Chemical Company, Inc., and used without further purification.

15. (CAUTION!) Some foaming occurs because of an exothermic reaction.

16. Litmus paper was used to determine the pH.

17. Gas chromatographic analysis of this material (6' x 1/8" 10% SP-2401 on 100-120 mesh supelcoport; 100-200°C program at 10°C/min; flow rate of 20 psi) showed the presence of ethyl decanoate, 2-undecanone, dimethyldiphenylsilane, and 2-methyl-2-undecanol in addition to the desired olefin. Small amounts of unidentified products were also present.

18. A mixture of hexanec (Mallinkrodt anhydrous) was used. If the crude product is placed directly on the silica gel column the column plugs and the compound does not elute.

19. Attempts to purify the product by spinning band distillation from the crude material gave only about 20% yield.

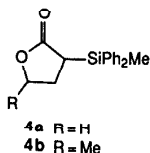
20. The product is greater than 97% pure by GLC (Note 17). It showed n_D^{20} 1.4360; ^1H NMR (CDCl_3 , 80 MHz) δ : 0.88 (brt. 3 H), 1.28 (brs. 12 H), 1.61 (brs, 3 H), 1.69 (brs, 3 H), 1.93-2.00 (m, 2 H), 5.14 (m, 1 H); ^{13}C NMR (CDCl_3) δ : 14.05, 17.62, 22.74, 25.64, 28.14, 29.41, 29.65, 29.99, 31.98, 125.08, 131.00; MS (70 eV) m/e (rel. abundance) 169 (2), 168 (14), 112 (6), 84 (11), 83 (13), 82 (6), 70 (23), 69 (100), 68 (10), 67 (13), 57 (34), 56 (68), 55 (34), 53 (9).

3. Discussion

Compound 1 represents one example of several α -(diphenylmethylsilyl) esters prepared by the method presented herein.³ Other examples include the α -diphenylmethylsilylated derivatives of ethyl acetate, ethyl propionate, ethyl 10-undecenoate, ethyl palmitate and ethyl stearate, all obtained in greater than 70% yield. Other alcohols, principally methyl, isopropyl, tert-butyl and 1-menthyl, also have been employed in this reaction without marked

differences. The reasons as to why the lithium enolates of esters are silylated at the carbon terminus with diphenylmethylchlorosilane as opposed to the usual silylation on the oxygen terminus is not clear. The direct C-silylation of the lithium enolates of α,β -disubstituted esters is not possible, except with ethyl cyclopropanecarboxylate and ethyl cyclobutanecarboxylate.⁴

The α -(diphenylmethylsilyl) esters have been shown to be vinyl cation equivalents **3**, and as such are precursors to terminal olefins and deuterated olefins,⁵ 1,1-disubstituted olefins⁶ and tri- and tetrasubstituted olefins.⁷ They are precursors to β -ketosilanes and ketones,⁸ wherein the overall transformation results in an ester to ketone conversion. They can also be deprotonated and the enolate anion condensed with aldehydes and ketones to give α,β -unsaturated esters,⁹ in particular α -alkylated- α,β -unsaturated esters.¹⁰ Their γ -lactone counterparts, α -(diphenylmethylsilyl)- γ -butyrolactone **4a** and α -(diphenylmethylsilyl)- γ -valerolactone **4b**, are precursors to 4-oxo acids,¹¹ 1,4-diketones¹² and α -ylidene- γ -lactones.¹³



1. Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Methyl-2-undecene: 2-Undecene, 2-methyl- (9); (56888-88-1)

Ethyl 2-(diphenylmethylsilyl)decanoate: Decanoic acid, 2-(methyl-diphenylsilyl)-, ethyl ester (11); (89638-16-4)

Ethyl decanoate: Decanoic acid, ethyl ester (8,9); (110-38-3)

Diphenylmethylchlorosilane: Silane, chloromethyldiphenyl- (8,9); (144-79-6)

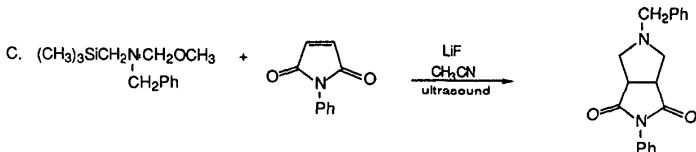
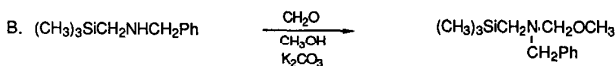
N-BENZYL-N-METHOXYMETHYL-N-(TRIMETHYLSILYL)METHYLAMINE

AS AN AZOMETHINE YLIDE EQUIVALENT:

2,6-DIOXO-1-PHENYL-4-BENZYL-1,4-DIAZABICYCLO[3.3.0]OCTANE

(Pyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione, tetrahydro-

2-phenyl-5-(phenylmethyl)-, cis-)



Submitted by Albert Padwa and William Dent.¹

Checked by Bruce Lefker and Albert I. Meyers.

1. Procedure

A. *N*-Benzyl-*N*-(trimethylsilyl)methylamine. An oven-dried, 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 12.58 g (0.1 mol) of chloromethyltrimethylsilane (Note 1). Benzylamine (Note 2) (33.1 g, 0.3 mol) is added with stirring and the resulting solution is heated at 200°C for 2.5 hr. At the end of this time a 0.1 N sodium hydroxide solution is added in order to hydrolyze the white organic salt that had formed. The mixture is extracted with ether

and the ether layer is dried over magnesium sulfate and concentrated under reduced pressure. The residue is distilled under reduced pressure through a 6-inch Vigreux column to give 11.6-15.3 g (58-72%) of N-benzyl-N-(trimethylsilyl)methylamine, bp 68-72°C (0.7-0.8 mm) (Note 3).

B. N-Benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine. A 25-mL, round-bottomed flask equipped with a stirring bar is charged with 6.0 g (74 mmol) of a 37% aqueous formaldehyde solution (Note 4). The solution is cooled to 0°C and 10.0 g (51.7 mmol) of N-benzyl-N-(trimethylsilyl)methylamine is added dropwise with stirring. After the solution is stirred for 10 min at 0°C, 6 mL (0.15 mol) of methanol (Note 5) is added in one portion. Potassium carbonate (4.0 g) is added to the mixture to absorb the aqueous phase. The mixture is stirred for 1 hr, the non-aqueous phase is decanted, an additional 2.0 g of potassium carbonate is added, and the mixture is stirred at 25°C for 12 hr. Ether is added to the mixture and the solution is dried over potassium carbonate, filtered, and concentrated under reduced pressure (Note 6). The residue is distilled at reduced pressure to give 6.8-8.6 g (54-69%) of N-benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine as a colorless liquid, bp 77-80°C (0.5 mm) (Note 7).

C. 2,6-Dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane. An oven-dried, 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 10.0 g (0.042 mol) of N-benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine and 100 mL of anhydrous acetonitrile (Note 8). N-Phenylmaleimide (Note 9) (7.3 g, 0.042 mol) is added followed by 1.7 g (0.063 mol) of lithium fluoride (Note 10). The reaction mixture is sonicated (Note 11) for 3 hr and poured into 100 mL of water. The mixture is extracted with three 100-mL portions of ether. The organic extracts are combined and washed with 100 mL of saturated sodium chloride solution, dried over magnesium

sulfate, filtered, and concentrated under reduced pressure. The residue is chromatographed on a silica gel column (300 g) using a 35% ethyl acetate-hexane mixture (ca. 1500 mL) as the eluant to give 9.2-9.6 g (72-75%) of 2,6-dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane as a pale yellow solid, mp 97-98°C (Note 12).

2. Notes

1. Chloromethyltrimethylsilane is purchased from Petrarch Systems, Inc. and is used without purification.

2. Benzylamine, purchased from Aldrich Chemical Company, Inc., is distilled and stored over potassium hydroxide.

3. The submitters report bp 89-90°C (5 mm). The ^1H NMR spectrum (CDCl_3 , 90 MHz) is as follows δ : 0.10 (s, 9 H), 2.00 (s, 2 H), 3.78 (s, 2 H) and 7.28 (s, 5 H).

4. Formaldehyde (37% solution in water) is purchased from Aldrich Chemical Company, Inc. Sufficient aqueous 10% sodium hydroxide solution (1-5 drops) is added until the pH reaches 7.

5. Purified grade methanol, purchased from Fisher Scientific Company, is used.

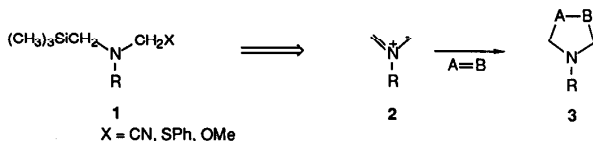
6. The submitters found it easier to pump down the crude mixture overnight under reduced pressure to ensure that all the methanol is removed. If not, the residue tends to bump uncontrollably upon distillation.

7. The spectral properties are as follows: IR (neat) cm^{-1} : 3095, 3064, 3030, 2900, 1605, 1495, 1450, 1422, 1385, 1362, 1245, 1070, 925, 845, 740 and 700; ^1H NMR (CDCl_3 , 90 MHz) δ : 0.10 (s, 9 H), 2.13 (s, 2 H), 3.20 (s, 3 H), 3.72 (s, 2 H), 3.95 (s, 2 H) and 7.22 (m, 5 H).

8. Anhydrous acetonitrile, purchased from Aldrich Chemical Company, Inc., is distilled over calcium hydride and stored over 4 Å molecular sieves.
9. N-Phenylmaleimide is purchased from Aldrich Chemical Company, Inc., and used without purification.
10. Lithium fluoride is purchased from Fisher Scientific Company.
11. A Branson ultrasonic cleaner (2.8 liter, 13 x 23 x 10 cm), purchased from Fisher Scientific Company, is used for sonication. Without sonication, the yield drops by ca. 10-15%.
12. The spectral properties are as follows: IR (neat) cm^{-1} : 3145, 3000, 2950, 2900, 2800, 1760, 1700, 1575, 1490, 1445, 1380, 1310, 1200, 1155, 880, 840, 740 and 700; ^1H NMR (CDCl_3 , 90 MHz) δ : 2.3-2.7 (m, 2 H), 3.2-3.6 (m, 4 H), 3.60 (s, 2 H) and 7.0-7.7 (m, 10 H).

3. Discussion

The preparation of pyrrolidines has received extensive attention by synthetic chemists in recent years, in part due to the interesting biological activities exhibited by several polysubstituted pyrrolidines.² Little attention has been given to one of the most conceptually simple ways of pyrrolidine formation: a 1,3-dipolar cycloaddition of an azomethine ylide with an olefin. This is not surprising since few methods exist for the preparation of nonstabilized azomethine ylides.³⁻¹³ Silyl-substituted amines of Type 1 represent conjunctive reagents which can be considered as the equivalent of a nonstabilized azomethine ylide. These reagents have recently been found to



undergo 1,3-dipolar cycloaddition to olefins to give pyrrolidine derivatives in good yield.¹⁴⁻¹⁶ The present procedure provides a convenient route for the synthesis of a variety of five-membered ring nitrogen heterocycles using different dipolarophiles. Some representative examples are given in Table I. Advantages of the present method over existing methodologies include mild conditions, high yield and simplicity of the cycloaddition. Trimethylsilyl triflate or trimethylsilyl iodide can also be used.¹² However, these reagents are expensive and require longer reaction times.

We have found that sonication of the reaction mixture decreases the time needed for reaction and also substantially increases the yield. This is probably related to an increase in the solubility of lithium fluoride in acetonitrile or is a consequence of surface effects on the metal.

N-Benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine undergoes stereospecific cycloaddition with dimethyl maleate and fumarate. The cycloaddition behavior of an unsymmetrically substituted α -methoxysilylamine has also been examined and found to occur with high overall regioselectivity. The stereospecificity and regioselectivity of the reaction is consistent with a concerted 1,3-dipolar cycloaddition reaction.¹⁷

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,6-Dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane:

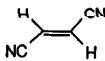
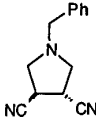
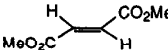
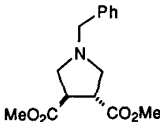
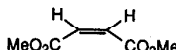
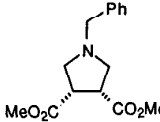
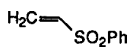
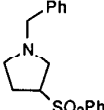

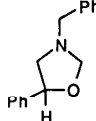

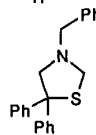
Pyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione, tetrahydro-2-phenyl-5-(phenylmethyl)-, cis- (11); (87813-00-1)

N-Benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine: Benzenemethanamine, N-(methoxymethyl)-N-[(trimethylsilyl)methyl]- (11); (93102-05-7)

N-Benzyl-N-(trimethylsilyl)methylamine: Benzenemethanamine, N-[(trimethylsilyl)methyl]- (9); (53215-95-5)

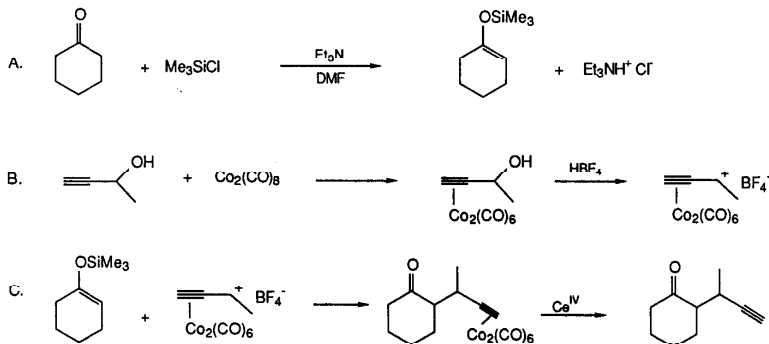
N-Phenylmaleimide: Maleimide, N-phenyl- (8); 1 H-Pyrrole-2,5-dione, 1-phenyl- (9); (941 69 5)

CYCLOADDITION OF 1 WITH ELECTRON-DEFICIENT DIPOLAROPHILES

Dipolarophile	Product	% Yield
		90
		90
		90
		92
		80
		91

ALKYLATIONS USING HEXACARBONYL (PROPARGYL IUM) DICOBALT SALTS:

2-(1-METHYL-2-PROPYNYL)CYCLOHEXANONE



Submitted by Valsamma Varghese, Manasi Saha, and Kenneth M. Nicholas.¹

Checked by T. V. RajanBabu, Leslie G. Upchurch, and Bruce E. Smart.

1. Procedure

Caution! Dicobalt octacarbonyl is highly toxic and air sensitive. All operations with this reagent should be carried out in an inert atmosphere and in a well-ventilated hood.

A. *1-Trimethylsiloxy-cyclohexene.*² A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum, and reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler. The system is flushed with nitrogen, flame dried, and while the

system is maintained under a static pressure of nitrogen, the flask is charged with 300 mL of dry dimethylformamide (Note 1) and 110.3 g (1.1 mol) of triethylamine (Note 2); 58.3 g (0.54 mol) of chlorotrimethylsilane (Note 3) is added by syringe. Cyclohexanone (40.0 g, 0.41 mol) (Note 4) is added and the mixture is refluxed with stirring for 48 hr. After the flask is cooled to room temperature, the contents are poured into 600 mL of pentane. The resulting mixture is transferred to a separatory funnel and washed with three 500-mL portions of cold aqueous sodium bicarbonate. The organic layer is washed rapidly in succession with 200 mL of cold 1.5 N hydrochloric acid and 200 mL of cold aqueous sodium bicarbonate. The pentane solution is dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product is distilled through a short Vigreux column to give 53-54 g (76-77%) of 1-trimethylsiloxycyclohexene as a colorless liquid, bp 75-80°C (20-21 mm) (Note 5)

B. *Hexacarbonyl(1-methyl-2-propynyl)dicobalt tetrafluoroborate*. 1. A 2-L, two-necked, round-bottomed flask fitted with a magnetic stirring bar, stopper, and gas inlet T-tube which is attached to a mineral oil bubbler is flame dried under a flow of nitrogen. The flask is charged with 200 mL of dry dichloromethane (Note 6) and 13.0 g (0.185 mol) of 3-butyne-2-ol (Note 7). After the mixture is stirred for 15 min, 65.0 g (0.19 mol) of dicobalt octacarbonyl (Note 8) is added in portions over a few minutes while maintaining a slow stream of nitrogen. Vigorous gas evolution (carbon monoxide!) is observed. The mixture is stirred for 4-5 hr, and the solvent is then removed under reduced pressure (20-25 mm). The residual solid (alkyne)- $\text{Co}_2(\text{CO})_6$ complex is dissolved in 40 mL of propionic anhydride under nitrogen and cooled to -45°C in a dry ice/acetonitrile bath. Tetrafluoroboric acid-dimethyl etherate (37.3 g, 0.28 mol) (Note 9) is added with stirring. After

30 min, 600-800 mL of anhydrous diethyl ether is added with continuous stirring. The burgundy red salt which precipitates is isolated by filtration under a flow of nitrogen (Note 10) and is thoroughly washed with anhydrous diethyl ether to give 60-61 g (76-77%) of hexacarbonyl(1-methyl-2-propynyl)dicobalt tetrafluoroborate. This material is used immediately in the following step.

C. *2-(1-Methyl-2-propynyl)cyclohexanone*. A 2-L, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, stopper, and pressure-equalizing dropping funnel fitted with a gas inlet T-tube that is connected to a mineral oil bubbler. The flask is flushed with nitrogen and charged with 150 mL of dry dichloromethane (Note 6) and 60.0 g (0.141 mol) of the salt from Part B. The mixture is stirred and cooled to -78°C in a dry ice/2-propanol bath, and 23.9 g (0.141 mol) of 1-trimethylsiloxy-cyclohexene (Part A) is added dropwise over a few minutes. The mixture is stirred at -78°C for 4 hr. After the solution is warmed to room temperature, dichloromethane is removed under reduced pressure and replaced with 400 mL of acetone. The dark red solution of the alkyne complex is cooled to -78°C and 175 g (0.32 mol) of ceric ammonium nitrate (Note 11) is added in portions. The mixture is stirred until the gas evolution (carbon monoxide!) ceases (ca. 4 hr) (Note 12). The reaction mixture is warmed to room temperature, poured into 1 L of saturated brine solution, and extracted with four 250-mL portions of diethyl ether. The combined ether extracts are dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residual red oil is distilled at reduced pressure to afford 15.0-15.2 g (71-72%) of 2-(1-methyl-2-propynyl)cyclohexanone as a pale yellow liquid, bp $57-60^{\circ}\text{C}$ (10 mm) (Note 13).

2. Notes

1. Dimethylformamide, obtained from Aldrich Chemical Company, Inc., was vacuum distilled from calcium hydride, bp 44°C (25 mm), and stored over 3 Å molecular sieves.

2. Triethylamine, obtained from the Aldrich Chemical Company, Inc., was distilled from potassium hydroxide prior to use.

3. Chlorotrimethylsilane, obtained from the Aldrich Chemical Company, Inc., was redistilled from calcium hydride before use.

4. Cyclohexanone was purchased from the Aldrich Chemical Company, Inc., redistilled, and stored over 4 Å molecular sieves.

5. The product is over 99.5% pure by GLPC (6' x 1/8" 3% SP 2100 on 100-120 mesh Supelcoport column) and has the following spectral characteristics: ^1H NMR (CDCl_3) δ : 0.21 (s, 9 H), 1.55 (m, 2 H), 1.69 (m, 2 H), 2.05 (br d, 4 H), 4.88 (br s, 1 H).

6. Dichloromethane, obtained from the Aldrich Chemical Company, Inc., was distilled from calcium hydride and stored over 4 Å molecular sieves.

7. 3-Butyn-2-ol was obtained from the Aldrich Chemical Company, Inc., and used without further purification.

8. Dicobalt octacarbonyl was obtained from Alfa Products, Morton/Thiokol, Inc. It is best weighed in a nitrogen-filled polyethylene glove bag or in a dry box.

9. Tetrafluoroboric acid-dimethyl etherate (d 1.38 g/mL) was purchased from the Aldrich Chemical Company, Inc. The submitters note that a tetrafluoroboric acid/acetic acid mixture, which is prepared by carefully adding 49% aqueous tetrafluoroboric acid (50 g, 0.28 mol) to ice-cold acetic anhydride (30.6 g, 0.30 mol), also can be used.

10. The filtration under nitrogen is conveniently carried out in a Schlenk filter flask.³

11. Ceric ammonium nitrate was obtained from the Aldrich Chemical Company, Inc.

12. The disappearance of the dark red (alkyne) $\text{Co}_2(\text{CO})_6$ complex can be monitored by TLC on silica gel with a 1:9 diethyl ether:petroleum ether solvent mixture.

13. The product is obtained as a 2:1 diastereomeric mixture and is over 99% pure by GLPC (6' x 1/8" 3% SP 2100 on 100-120 mesh Supelcoport column). It has the following spectral characteristics: IR (CCl_4) 1710 cm^{-1} ; ^1H NMR (CDCl_3) δ : 0.8-2.9 (br envelope, 10 H), 1.05 (d, 3 H, $J = 7$, minor diastereomer), 1.10 (d, 3 H, $J = 7$, major diastereomer), 2.15 (s, 1 H, both diastereomers); ^{13}C NMR (CDCl_3) δ : 16.3, 19.2, 24.2, 25.6, 24.7, 27.1, 28.4, 30.7, 41.7, 41.9, 54.1, 54.8, 68.2, 69.6, 86.3, 87.5, 209.7, 210.3; MS (70 eV) m/e 150, 121 (100%).

3. Discussion

In addition to their reactions with trimethylsilyl enol ethers, (propargylium) $\text{Co}_2(\text{CO})_6^+$ complexes react with a variety of other mild carbon nucleophiles including activated aromatic compounds,⁴ β -dicarbonyl compounds,⁵ other enol derivatives (enol acetates and ketones directly),⁶ allylsilanes,⁷ and alkyl- and alkynyl-aluminum reagents.^{8,9} These reactions provide a flexible means to introduce the synthetically versatile propargyl function. Key features of propargylations using these complexes are: 1) ready introduction and removal of the activating and directing $-\text{Co}_2(\text{CO})_6$ group; 2) regiospecific attack by nucleophiles at the carbon α to the coordinated

alkynyl group, giving propargyl products only (no allenic co-products); and 3) very mild reaction conditions and good overall yields.

The method reported here appears to be the one of choice for the dependable, efficient α -propargylation of ketones. It can be applied to propargylate ketones regioselectively at either the less substituted α -position (via the trimethylsilyl enol ether) or the more substituted α -position (using the enol acetate or even the ketone directly⁶). The resulting α -propargylated ketones are very useful synthetic intermediates. They have been converted to chromanols,¹⁰ furans,¹¹ other heterocycles,¹¹ and cyclohexenones,¹² and they undergo regiospecific hydration to 1,4-diketones which, in turn, can be converted to cyclopentenones.¹³⁻¹⁵ More classical indirect ketone propargylations generally give low yields with substantial co-production of allenic by-products, as with enamine^{10,16} or acetoacetic ester propargylations.^{11,17} Direct coupling of ketone enolates with propargyl halides or tosylates have rarely been attempted and can be expected to suffer the same limitations.

This preparation of 2-(1-methyl-2-propynyl)cyclohexanone appears to be the first reported.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Trimethylsiloxycyclohexene: Silane, (1-cyclohexen-1-yloxy)trimethyl-
(8,9); (6651-36-1)

Hexacarbonyl(1-methyl-2-propynyl)dicobalt tetrafluoroborate: Cobalt(1+),
hexacarbonyl[μ -[2,3,- η :2,3- η]-1-methyl-2-propynyl]di-, (Co-Co),
tetrafluoroborate(1-) (10); (62866-98-2)

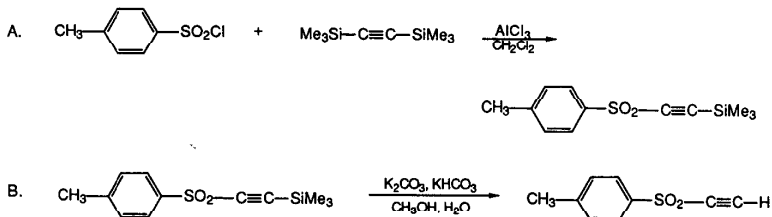
3-Butyn-2-ol: 3-Butyn-2-ol, (\pm)- (10); (65337-13-5)

Dicobalt octacarbonyl: Cobalt, octacarbonyldi-, (Co-Co) (8,9); (15226-74-1)

Tetrafluoroboric acid-dimethyl etherate: Borate(1-), tetrafluoro-, hydrogen, compd. with oxybis[methane] (1:1) (10); (67969-83-9)

Ceric ammonium nitrate: Cerate(2-), hexanitrate-, diammonium (8); Cerate(2-), hexakis(nitrato-0)-, diammonium, (OC-6-11)- (9); (16774-21-3)

ETHYNYL p-TOLYL SULFONE
(Benzene, 1-(ethynylsulfonyl)-4-methyl-)



Submitted by Liladhar Waykole and Leo A. Paquette.¹

Checked by Dirk A. Heerding and Larry E. Overman.

1. Procedure

A. *p*-Tolyl 2-(trimethylsilyl)ethynyl sulfone. In a flame-dried, 500-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet and glass stoppers are placed 200 mL of dry dichloromethane (Note 1) and 29.4 g (0.22 mol) of freshly powdered anhydrous aluminum chloride. After the addition of *p*-toluenesulfonyl chloride (41.9 g, 0.22 mol), the resulting dark brown mixture is shaken occasionally for 20 min at room temperature.

A 1-L, three-necked, round-bottomed flask equipped with a 500-mL addition funnel and a Teflon-coated stirring bar is flame-dried under a stream of dry nitrogen. The flask is charged with bis(trimethylsilyl)acetylene (34.0 g, 0.20 mol) (Note 2) and dry dichloromethane (200 mL) (Note 1) and the solution is cooled to 0°C in an ice-water bath.

The p-toluenesulfonyl chloride-aluminum chloride complex is quickly filtered through a glass-wool plug (Note 3) into the addition funnel. The residue is washed rapidly with an additional 50 mL of dry dichloromethane and the funnel is quickly stoppered. The complex is added dropwise during 1 hr to the cold (0°C), magnetically stirred silylacetylene solution. Upon completion of the addition, the reaction mixture is allowed to warm to room temperature and is stirred for an additional 12 hr. The mixture is hydrolyzed by pouring it into a slurry of 20% hydrochloric acid (200 mL) and ice (200 g) (Note 4). The organic layer is separated, washed twice with water (150 mL), and dried over anhydrous sodium sulfate. Removal of solvent in a rotary evaporator gives a brown solid (Note 5) which is recrystallized from light petroleum ether (bp 40-60°C) to yield 39.7-40.4 g (79-80%) of p-tolyl 2-(trimethylsilyl)ethynyl sulfone as white crystals, mp 81-82°C (Note 6).

B. *Ethynyl p-tolyl sulfone*. A 1-L, three-necked, round-bottomed flask equipped with a thermometer, 500-mL addition funnel, nitrogen inlet, and Teflon-coated magnetic stirring bar is charged with p-tolyl 2-(trimethylsilyl)ethynyl sulfone (25.2 g, 0.1 mol) and 300 mL of reagent grade methanol. After the mixture is stirred for 30 min, a clear solution is obtained. In the addition funnel is placed 350 mL of an aqueous solution containing potassium carbonate (6.2×10^{-3} M) and potassium bicarbonate (6.2×10^{-3} M); this buffer is added at a rate to maintain the reaction temperature at 30°C (Notes 7 and 8). The mixture is diluted with water (200 mL), and extracted with four 100-mL portions of chloroform. The combined organic phases are washed three times with water (100 mL) and twice with brine (100 mL) prior to drying over anhydrous sodium sulfate. Removal of solvent under reduced pressure leaves a creamy white solid, which is purified either by recrystallization from ethyl acetate-petroleum ether or by silica gel

chromatography using 10% ethyl acetate in petroleum ether as eluant (Note 9). There is obtained 15.0 g (83%) of colorless crystals, mp 74-75°C (Notes 10 and 11).

2. Notes

1. The submitters used dichloromethane freshly distilled from powdered calcium hydride.

2. This reagent was obtained from Petrarch Systems, Inc., Bartram Road, Bristol, PA 19007.

3. This mixture is rather hygroscopic and must be maintained under a nitrogen atmosphere as much as possible.

4. Stirring facilitates the hydrolysis. The reaction mixture should be added relatively slowly since the decomposition is exothermic.

5. Material of this purity may be used directly in the ensuing step. However, lower yields are realized.

6. Earlier citations^{2,3} report mp 81-82°C. This product has the following spectral properties: IR (KBr) cm^{-1} : 2124, 1338, 1164, 854, 779; ^1H NMR (CDCl_3) δ : 0.22 (s, 9 H), 2.48 (s, 3 H), 7.40 (d, 2 H, $J = 9$), 7.91 (d, 2 H, $J = 9$). MS (CI, 70 eV, isobutane) 253 ($M + 1$, 100). Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{O}_2\text{SSi}$: C, 57.10; H, 6.40; S, 12.70. Found: C, 57.84; H, 5.88; S, 12.85. The checkers found that treatment of the crude solid with activated charcoal is required to obtain colorless product.

7. The checkers found that the reaction is complete immediately after addition if the temperature is maintained accurately at 30°C. The reaction rate is dramatically dependent on the reaction temperature. The submitters report that considerable resinous material is obtained if the temperature goes above 30°C.

8. This period of reaction may vary depending on the scale of the reaction. Progress may be easily followed by isolating aliquots and obtaining ^1H NMR spectra. The disappearance of the trimethylsilyl singlet is the observable diagnostic.

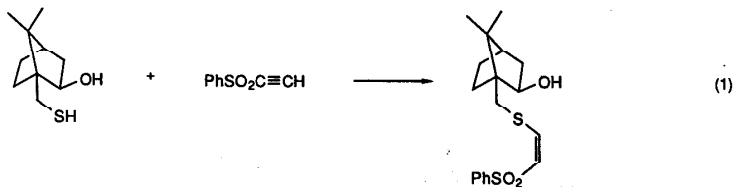
9. The checkers found that an impurity with a characteristic ^1H NMR singlet at 3.74 ppm is readily removed by recrystallization, but cannot be removed by chromatography. They also report that small amounts of this impurity are formed during flash chromatography on silica gel.

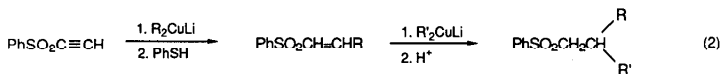
10. The ^1H NMR spectral characteristics of this sulfone are as follows (CDCl_3) δ : 2.47 (s, 3 H), 3.52 (s, 1 H), 7.38 (dd, 2 H, $J = 8.5, 0.6$), 7.88 (d, 2 H, $J = 8.5$). Its IR spectrum (KBr) consists of the following bands (cm^{-1}): 3235, 2013, 1337, 1156. MS (CI, 70 eV, isobutane) 181 ($M + 1$, 100). Anal. Calcd. for $\text{C}_9\text{H}_8\text{SO}_2$: C, 59.97, H, 4.47, S, 17.79. Found: C, 59.20; H, 4.55; S, 17.52.

11. Further purification can be achieved if desired by recrystallization of this material from hexane-ethyl acetate (95:5). Shiny needles which melt at 75°C are thereby obtained.

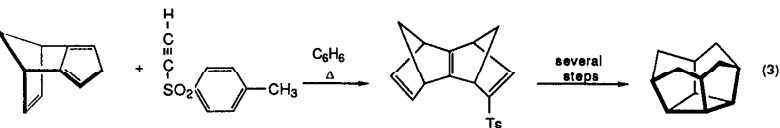
3. Discussion

Interest in arylsulfonyl acetylenes arose initially because of their powerful Michael acceptor properties. Examples of facile nucleophilic addition involving thiolates (eq. 1),⁴⁻⁷ amines,² cuprates (eq. 2),⁸ malonate

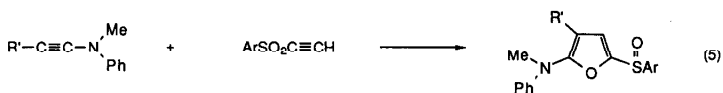
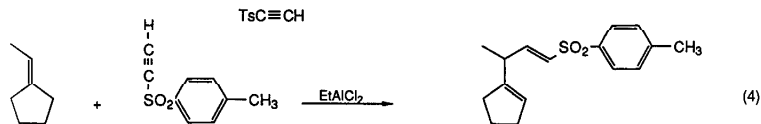




anions,⁹ alkoxides,^{10,11} hydroxylamines,^{12,13} and azlactone enolates¹⁴ abound. More recently, the dienophilic properties of this class of compounds have been used to advantage, e.g., use of the title compound as an acetylene synthon in Diels-Alder cycloadditions,^{15,16} its [4+2] capture by N-methoxycarbonylpyrrole in a first step toward the elusive 7-azanorbornadiene,¹⁷ and its pivotal role in a synthesis of [4]-peristylane (eq. 3).¹⁸ Ethynyl p-tolyl sulfone undergoes EtAlCl_2 -catalyzed ene reactions with alkenes to give



1,4-dienyl p-tolyl sulfones (eq. 4).¹⁹ Condensations with ynamines to give 2-amino-5-arylsulfinylfurans (eq. 5) have been reported.²⁰ α,β -Acetylenic sulfones also react with organolithium and Grignard reagents to give the correspondingly higher acetylene (eq. 6).²¹





The procedures used most often for preparation of arylsulfonyl acetylenes involve oxidation of the corresponding ethynyl thio ether. The thio ethers are usually obtained via a two-step sequence beginning with two-fold thiophenoxide displacement of chloride ion from cis-1,2-dichloroethylene, followed by elimination with n-butyllithium in the resultant cis-1,2-bisarylthioethylene.¹⁹ Less well known methods involve diazotization of 4-arylsulfonyl-5-aminoisoxazoles,²² dehydrobromination of cis- and trans-2-bromovinyl phenyl sulfone with fluoride ion,²³ and oxidative elimination of β -(phenylseleno)vinyl sulfones.²⁴ The method described here, which bypasses the need for strongly basic conditions, is adapted from the work of Bhattacharya, Josiah, and Walton.³ The simplicity and mildness of the method suggest that it may be broadly useful.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethynyl p-tolyl sulfone: Sulfone, ethynyl p-tolyl (8); Benzene, 1-(ethynylsulfonyl)-4-methyl- (9); (13894-21-8)

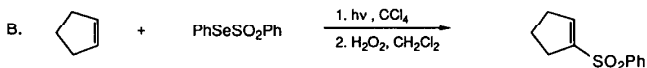
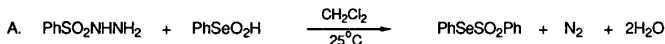
p-Tolyl 2-(trimethylsilyl)ethynyl sulfone: Silane, trimethyl [[(4-methylphenyl)sulfonyl]ethynyl]- (9); (34452-56-7)

Bis(trimethylsilyl)acetylene: Silane, 1,2-ethynediylbis[trimethyl- (9); (14630-40-1)

DIENOPHILE ACTIVATION VIA SELENOSULFONATION:

1-(BENZENESULFONYL)CYCLOPENTENE

(Benzene, (1-cyclopenten-1-ylsulfonyl)-)



Submitted by Ho-Shen Lin, Michael J. Coghlan, and Leo A. Paquette.¹

Checked by Tony Haight and Edwin Vedejs.

1. Procedure

A. *Phenyl benzeneselenosulfonate*. A 1-L, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 250-mL addition funnel containing 17.2 g (100 mmol) of benzenesulfonyl hydrazide (Note 1) and 125 mL of dichloromethane is charged with 18.9 g (100 mmol) of phenylseleninic acid (Note 1) and 125 mL of dichloromethane. The seleninic acid is stirred at 25°C as the hydrazide slurry is added over 1 hr (Note 2). After an additional hour at 25°C, the reaction mixture is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is dissolved in 250 mL of hot methanol and the solution of selenosulfonate is cooled overnight at ~5°C in a refrigerator to induce crystallization. The yellow product which precipitates is filtered and recrystallized from methanol to afford 24.3–25.2 g (83–85%) of phenyl benzeneselenosulfonate, mp 56°C (Note 3).

B. 1-(Benzenesulfonyl)cyclopentene. A one-necked, flat-bottomed, cylindrical flask (5 cm in diameter and 23 cm in height) equipped with a Teflon-coated magnetic stirring bar is charged in turn with phenyl benzeneselenosulfonate (15.0 g, 50.5 mmol), carbon tetrachloride (160 mL), and cyclopentene (11.1 mL, 126 mmol) (Note 4). The flask is equipped with a Friedrichs condenser and the stirred reaction mixture is blanketed with nitrogen. Following irradiation with a 150W sunlamp at room temperature for 45 min, the solution is transferred to a 500-mL, one-necked, round-bottomed flask and concentrated on a rotary evaporator.

A Teflon-coated magnetic stirring bar is placed atop the residue, which is dissolved in 140 mL of dichloromethane. The stirred solution is cooled in an ice-water bath to 0°C as 60 mL of 15% hydrogen peroxide is added dropwise via an addition funnel over 30 min (Note 5). Vigorous stirring is maintained at this temperature for 1.5 hr. The mixture is transferred to a 1-L separatory funnel, diluted with 400 mL of ethyl acetate and washed twice with 150-mL portions of water. The organic layer is dried over anhydrous magnesium sulfate, filtered, and freed of solvent under reduced pressure. The residual yellowish solid is dissolved in a small amount of dichloromethane and eluted with 5% ethyl acetate in dichloromethane through a column of 80 g of neutral alumina (activity III) to afford 8.28-9.19 g (79-87%) of colorless crystals, mp 65-66°C. ¹H NMR analysis shows this material to be of very high purity (Note 6).

2. Notes

1. Benzenesulfonyl hydrazide is available from the Fluka Chemical Company, 255 Oser Avenue, Hauppauge, NY 11788.

2. This addition time ensures a slow, steady evolution of nitrogen during admixture of both slurried reactants.

3. Although this selenosulfonate is temperature and light sensitive, it can be stored indefinitely at refrigerator temperatures in an opaque glass container.²

4. Cyclopentene was purchased from the Aldrich Chemical Company, Inc. and used without further purification.

5. The peroxide is added at such a rate that the mildly exothermic oxidation/elimination reaction is well controlled. Faster addition of hydrogen peroxide can result in uncontrollable foaming.

6. The product has the following spectral properties: IR (KBr) cm^{-1} : 3060, 2960, 2920, 2840, 1610, 1580, 1440, 1300, 1150, 1085, 935, 825, 745, 710, 680, 600; ^1H NMR (CDCl_3) δ : 1.8-2.2 (m, 2 H, $\text{CH}_2\text{CH}_2\text{-CH}_2$), 2.2-2.6 (m, 4 H, $\text{CH}_2\text{C=}$), 6.6 (br s, 1 H, $=\text{CH}$), 7.3-8.0 (m, 5 H); m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$: 208.0558; Found 208.0553. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$: C, 63.43, H, 5.81. Found: C, 63.49; H, 5.83.

3. Discussion







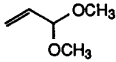
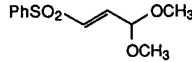


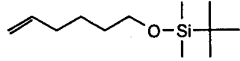
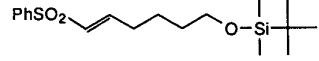
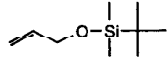
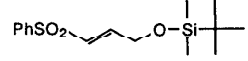
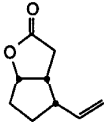
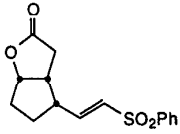
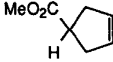
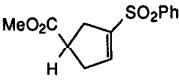

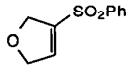
Recent investigations into the chemistry of vinyl sulfones have revealed that they are versatile synthetic intermediates, serving either as dienophiles³ or Michael acceptors.⁴ Methods for the preparation of vinyl sulfones from unactivated olefins have customarily involved the catalyzed (boron trifluoride or benzoyl peroxide) addition of PhSO_2X ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{or SePh}$), followed by elimination of HX .⁵ However, when phenylsulfonyl halides are employed, yields are variable, reactions are frequently incomplete, and the Lewis acid or free-radical catalyst employed can potentially interfere

with other functionality present. On the other hand, the selenosulfonation method, particularly when photochemically induced,^{3,6} proceeds smoothly to completion in high yield and is compatible with several functional groups (Table I).³ A further consequence of the trans disposition of the benzeneselenenyl and benzenesulfonyl groups is invariant elimination to give the α,β -unsaturated sulfone.

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TABLE

PHOTOINDUCED SELENOSULFONATION-ELIMINATION OF OLEFINS

Olefin	Product	Yield (%)
		62
		89
		84
		73
		93
		89
		65
		72
		90
		75

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-(Benzenesulfonyl)cyclopentene: Benzene, (1-cyclopenten-1-ylsulfonyl)- (10);
(64740-90-5)

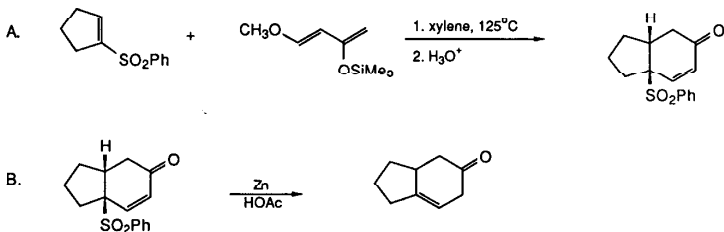
Phenyl benzeneselenosulfonate: Benzenesulfonoselenoic acid, Se-phenyl ester
(9); (60805-71-2)

Benzenesulfonyl hydrazide: Benzenesulfonic acid, hydrazide (0.9);
(80-17-1)

Phenylseleninic acid: Benzeneseleninic acid (8,9); (6996-92-5)

Cyclopentene (8,9); (142-29-0)

REDUCTIVE ANNULATION OF VINYL SULFONES: BICYCLO[4.3.0]NON-1-EN-4-ONE
(5H-Inden-5-one, 1,2,3,3a,4,6-hexahydro-)



Submitted by Ho-Shen Lin and Leo A. Paquette.¹

Checked by Edward J. Adams and Edwin Vedejs.

1. Procedure

A. *4-Oxo-1-(benzenesulfonyl)-cis-bicyclo[4.3.0]non-2-ene*. A 250-mL, one-necked flask equipped with a Teflon-coated magnetic stirring bar, condenser, and nitrogen inlet tube is charged with 8.76 g (42.1 mmol) of 1-(benzenesulfonyl)cyclopentene (Note 1), 8.75 g (50.9 mmol) of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene and 8 mL of xylene (Note 2). The stirred reaction mixture is blanketed with nitrogen and heated in an oil bath at 123–125°C in the dark for 3 days. After the solution is cooled, it is diluted with 80 mL of tetrahydrofuran and 30 mL of 2 N hydrochloric acid and heated at reflux temperature for 24 hr. Most of the tetrahydrofuran is removed on a rotary evaporator. The residue is transferred to a 1-L separatory funnel and diluted with ether (200 mL) and dichloromethane (100 mL). The organic phase

is washed with two 50-mL volumes of half-saturated sodium bicarbonate solution and a mixed solution of saturated sodium bicarbonate (10 mL) and half-saturated sodium chloride (40 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue is subjected to flash column chromatography on silica gel (250 g). Elution with a mixture of ethyl acetate-dichloromethane-petroleum ether (1:25:25) returns 3.56 g (41%) of unreacted 1-(benzenesulfonyl)cyclopentene. Subsequent increase in the solvent polarity to 3:25:25 provides the cycloadduct as a yellowish solid. This material is dissolved in the minimum amount of dichloromethane to which is added 25 mL of ether; 4.33 g of colorless crystals precipitate. Concentration of the filtrate and crystallization from ether-petroleum ether afford an additional 0.77-1.34 g of light yellow crystals (combined yield of 44-49%) (Note 3).

B. *Bicyclo[4.3.0]non-1-en-4-one*. The preceding enone (5.64 g, 20.4 mmol) is dissolved with magnetic stirring in 120 mL of glacial acetic acid contained in a 500-mL, one-necked flask. Zinc powder (13.3 g, 0.203 mol) (Note 4) is introduced and the capped reaction mixture is stirred vigorously at room temperature for 1 hr. The zinc is removed by suction filtration through a Celite pad (Büchner funnel) and washed with 200 mL of ether. The combined filtrates are transferred to a 2-L separatory funnel, diluted with 300 mL of petroleum ether, and washed with 200 mL of water. The aqueous phase is reextracted with 300 mL of a 1:1 mixture of ether and petroleum ether. Finally the combined organic layers are washed with 200 mL of water and 200 mL of saturated sodium bicarbonate solution prior to drying over anhydrous magnesium sulfate and filtration. The solvents are removed on a rotary evaporator to leave a pale yellow oil which is purified by chromatography on silica gel (elution with 14% ethyl acetate in petroleum ether). There is isolated 1.81-1.98 g (65-71%) of the β,γ -enone as a colorless oil (Notes 5 and 6).

2. Notes

1. See the preceding procedure for preparation of this intermediate.

2. The reagents were purchased from the Aldrich Chemical Company, Inc.; the diene was used without further purification, and xylene was dried by azeotropic removal of water and distillation from calcium hydride. 1-Methoxy-3-trimethylsiloxy-1,3-butadiene can be prepared by the method of *Org. Synth.* 1983, 61, 147.

3. The product can be further purified by crystallization from dichloromethane and ether. The crystalline modification that is obtained melts at 122.5-126°C. Melting and resolidification provides a second modification that melts at 122.5-123.2°C. The product has the following spectral properties: IR (CH_2Cl_2) cm^{-1} : 1680, 1310, 1150, 1090; ^1H NMR (CDCl_3) δ : 1.27-1.49 (m, 1 H), 1.55-1.87 (m, 3 H), 1.95-2.15 (m, 1 H), 2.16-2.31 (m, 2 H), 2.59-2.76 (m, 1 H), 2.93-3.13 (m, 1 H), 6.08 (d, 1 H, $J = 10.2$), 6.49 (dd, 1 H, $J = 10.0$, 1.7), 7.53 (br t, 2 H, $J = 7.3$), 7.64 (br t, 1 H, $J = 7.2$), 7.83 (br d, 2 H, $J = 7.2$); ^{13}C NMR (CDCl_3) δ : 22.76, 32.34, 35.68, 37.91, 38.73, 70.46, 129.05, 129.64, 131.89, 134.19, 136.38, 143.54, 196.27; m/z Calcd for $\text{M}^+-\text{C}_6\text{H}_5\text{SO}_2$: 135.0801; Found 135.0835. Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3\text{S}$: C, 65.19; H, 5.84. Found: C, 65.28, H, 5.85.

4. Fresh Mallinckrodt zinc dust was used without purification.

5. The product has the following spectral properties: IR (CH_2Cl_2) cm^{-1} : 2960, 2880, 1710; ^1H NMR (CDCl_3) δ : 1.08-1.35 (m, 1 H), 1.43-1.68 (m, 1 H), 1.68-1.91 (m, 1 H), 1.91-2.15 (m, 2 H), 2.15-2.38 (m, 2 H), 2.38-2.65 (m, 2 H), 2.65-2.94 (m, 2 H), 5.38-5.53 (m, 1 H); ^{13}C NMR (CDCl_3) δ : 24.86, 29.78, 33.80, 39.09, 40.40, 45.07, 113.22, 146.32, 211.05; m/z Calcd for $\text{C}_9\text{H}_{12}\text{O}$: 136.0888; Found 136.0896.

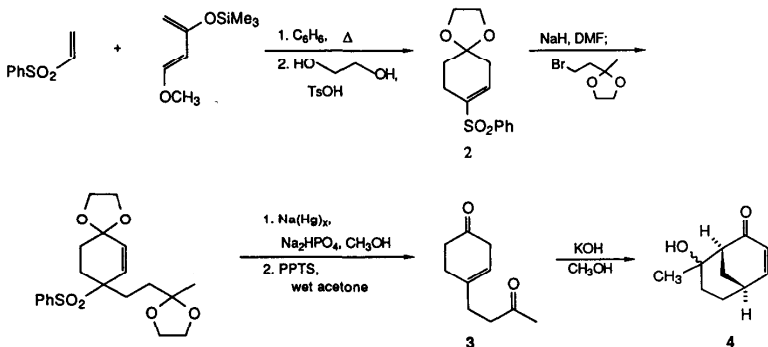
6. The product may be isolated by distillation, although two complications arise. First, because of the volatility of the enone, some material loss is incurred (yields of 57-60% result), bp 68-78°C (19 mm). More critically, heating induces some equilibration (generally about 10-15%) to the α,β -enone isomer. Thus, distillation should be avoided if pure β,γ -enone is desired. The spectral properties of the conjugated ketone, which can be obtained in a pure state by silica gel chromatography, are: IR (CH_2Cl_2) cm^{-1} : 2950, 2875, 1670; ^1H NMR (CDCl_3) δ : 1.31-1.49 (m, 1 H), 1.57-2.08 (m, 5 H), 2.40 (dd, 1 H, $J = 17.8, 7.4$), 2.47-2.62 (m, 2 H), 2.72-2.84 (m, 1 H), 5.92 (dd, 1 H, $J = 10.2, 2.1$), 6.70 (dd, 1 H, $J = 10.2, 3.5$); m/z Calcd for $\text{C}_9\text{H}_{12}\text{O}$: 136.0888; Found 136.0864.

3. Discussion

As a group, annulation reactions have been exceedingly valuable to the synthetic organic chemist. Unfortunately, processes of this type involving simple alkenes and cycloalkenes are few. However, the facility with which unactivated olefins can be transformed into vinyl sulfones,^{2,3} the high degree to which α,β -unsaturated sulfones are captured regioselectively by unsymmetrical dienes⁴ such as those developed by Danishefsky,⁵ and the ease with which reductive desulfonylation can be effected,^{6,7} combine to permit convenient synthetic entry to substituted cyclohexenones. Several representative examples can be found in Table I.

Other variants on this theme are possible. Thus, if the initially-formed Diels-Alder adduct is directly ketalized as in 2, the derived α -sulfonyl carbanion can be alkylated. Reductive desulfonylation and acidic hydrolysis (with pyridinium *p*-toluenesulfonate, PPTS) then deliver a 4-substituted

cyclohexenone (e.g., 3), which in many cases can be made to undergo further useful synthetic transformations (e.g., 4).⁴



The expandibility of the scheme allows one to prepare 4-substituted and 4,5-disubstituted 2(and 3)-cyclohexenones where the nature of the side chains can be widely varied.

1. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

- 1-(Benzenesulfonyl)cyclopentene: Benzene, (1-cyclopenten-1-ylsulfonyl)- (10); (64740-90-5)
- 1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene: Silane, [(3-methoxy-1-methylene-2-propenyl)oxy]trimethyl- (9); (59414-23-2)

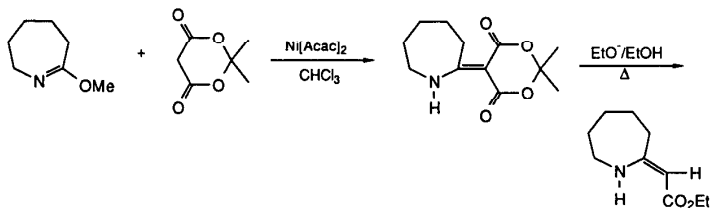
TABLE
REDUCTIVE ANNULATION OF VINYL SULFONES⁴

Starting material	Diene	Product	α,β,γ Ratio
	1b		100:0
	1b		100:0
	1b		60:40
	1a		0:100
	1b		0:100
	1a		0:100

^aIncluding an intermediate alkylation step.

ETHYL α -(HEXAHYDROAZEPINYLIDENE-2)ACETATE FROM O-METHYLCAPROLACTIM
AND MELDRUM'S ACID

(Acetic acid, (hexahydro-2H-azepin-2-ylidene)-, ethyl ester, (L)-)



Submitted by J. P. Celerier, E. Deloisy-Marchalant, G. Lhommet,
and P. Maitte.¹

Checked by Ting-Zhong Wang and Leo A. Paquette.

1. Procedure

A. *Isopropylidene α -(hexahydroazepinyldene-2)malonate.* In a 1-L, round-bottomed flask fitted with an efficient reflux condenser and equipped with a magnetic stirrer are placed 50.8 g (0.40 mol) of O-methylcaprolactim (Note 1), 57.6 g (0.40 mol) of Meldrum's acid (Note 2) and 0.25 g of nickel acetylacetonate monohydrate (Note 3) in 500 mL of anhydrous chloroform. The reaction mixture is refluxed for 12 hr. The solvent is removed with a rotary evaporator and the bright yellow precipitate is recrystallized from absolute ethanol to give 77-78 g (81-82%) of pale yellow crystals, mp 147-149°C (Note 4)

B. *Ethyl α -(hexahydroazepinylidene-2)acetate.* A solution of sodium ethoxide is prepared from 8.3 g (0.36 mol) of freshly cut sodium and 600 mL of freshly distilled absolute ethanol (Note 5) in a 1-L, round-bottomed flask equipped with a magnetic stirrer and fitted with a reflux condenser. To the stirred solution is added in one portion 71.7 g (0.30 mol) of freshly recrystallized isopropylidene α -(hexahydroazepinylidene-2)malonate. The mixture is refluxed and a white precipitate begins to appear. Refluxing is continued for 12 hr. The solvent is removed with a rotary evaporator and the white precipitate is placed in a 2-L beaker. Water (300 mL) is added and a 1 N hydrochloric solution is added dropwise to pH 6. The reaction mixture is extracted with four 100-mL portions of chloroform. The extracts are dried over anhydrous sodium sulfate and the solvent is removed with a rotary evaporator. The yellow solid residue is recrystallized from methanol to give 43-44 g (78-80%) of white powder, mp 55-56°C (Note 6).

2. Notes

1. O-Methylcaprolactim, (1-aza-2-methoxy-1-cycloheptene), is available from the Janssen Chimica Society (France) and from the Aldrich Chemical Company, Inc. It may be also prepared from ϵ -caprolactam and dimethyl sulfate.²

2. Meldrum's acid, (2,2-dimethyl-1,3-dioxane-4,6-dione), is available from the Janssen Chimica Society (France) or can be prepared from malonic acid and acetone.³ The checkers purchased Meldrum's acid from the Aldrich Chemical Company, Inc.

3. Nickel acetylacetonate monohydrate is a better basic catalyst than triethylamine for the condensation of Meldrum's acid and the lactim ether. The yields are higher and the product is easier to purify.

4. The submitters report mp 145-147°C.

5. Absolute ethanol must be freshly distilled to obtain good yields in the transesterification.

6. The submitters report mp 48-50°C. The product, ethyl α -(hexahydroazepinylidene-2)acetate, shows a Z geometry. The ^1H NMR (300 MHz) spectrum of this compound is as follows: δ : 1.22 (t, 3 H, $J = 7.1$), 1.65 (m, 6 H), 2.25 (m, 2 H), 3.25 (m, 2 H), 4.06 (q, 2 H, $J = 7.1$), 4.42 (s, 1 H), 8.83 (br s, 1 H).

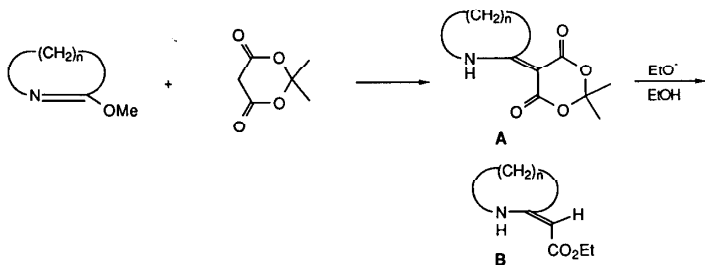
3. Discussion

This procedure is representative of a general and versatile method for the preparation of cyclic β -enamino esters which are known to be precursors of many alkaloids such as camptothecin,⁴ (\pm)-lamprolobine,⁵ (\pm)-lupinine⁶ or isoretronecanol.⁷

Common synthetic methods for the preparation of cyclic β -enamino esters are the condensation between a lactim ether and benzyl cyanoacetate followed by hydrogenolytic decarboxylation,⁸ or the imino ester carbon-carbon condensation with tert-butyl cyanoacetate followed by a trifluoroacetic acid treatment.⁹ The use of a thiolactam condensed with ethyl bromoacetate gives, after sulfur extrusion by triphenylphosphine,¹⁰ cyclic β -enamino esters. Compared with these methods, the Meldrum's acid condensation followed by the monodecarboxylating transesterification described here is more convenient and practical. An extension of this procedure permits preparation of smaller

cyclic β -enamino esters in comparable yields.¹¹ The results are reported in the Table below.

TABLE
PREPARATION OF SMALL-RING β -ENAMINO ESTERS



Product	n	Yield	mp (solvent)	References
			or bp/mm	
A	3	92-94%	170-172°C (ethanol)	11
B	3	85-87%	61-63°C (hexane)	2,7,11
A	4	90-92%	118-120°C (ethanol)	11
B	4	80-84%	90-94°C/0.1 mm	2,5,6,11

Only ethyl or methyl esters can be prepared by this procedure. However, pyrolysis of the cyclic β -enamino diesters at 225°C in the presence of different alcohols, thiols, or amines is a versatile and rapid method for preparing cyclic β -enamino esters, thioesters or amides.²

1. Laboratoire de Chimie des Hétérocycles and U.A. 455. Université P et M. Curie, Paris, France.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl α -(hexahydroazepinylidene-2)acetate: Acetic acid, (hexahydro-2H-azepin-2-ylidene)-, ethyl ester, (Z)- (10); (70912-51-5)

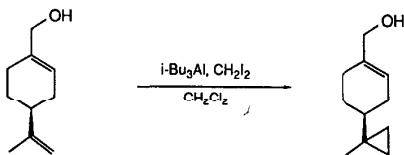
Isopropylidene α -hexahydroazepinylidene-2)malonate: 1,3-Dioxane-4,6-dione, 5-(hexahydro-2H-azepin-2-ylidene)-2,2-dimethyl- (10); (70912-54-8)

O-Methylcaprolactim: 2H-Azepine, 3,4,5,6-tetrahydro-/-methoxy- (8,9); (2525-16-8)

Meldrum's Acid: 2,2-Dimethyl-1,3-dioxane-4,6-dione: Malonic acid, cyclic isopropylidene ester (8); 1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

Nickel acetylacetonate: Nickel, bis(2,4-pentanedionato)- (8); Nickel, bis(2,4-pentanedionato-0,0')-, (SP-4-1) (9); (3264-82-2)

SELECTIVE CYCLOPROPANATION OF (S)-(-)-PERILLYL ALCOHOL:
 1-HYDROXYMETHYL-4-(1-METHYLCYCLOPROPYL)-1-CYCLOHEXENE
 (1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)-)



Submitted by Keiji Maruoka, Soichi Sakane, and Hisashi Yamamoto.¹

Checked by Hisatoyo Kato and Ryoji Noyori.

1. Procedure

A dry, 1-L, three-necked, round-bottomed flask is equipped with a gas inlet, 50-mL pressure-equalizing dropping funnel, rubber septum, and a Teflon-coated magnetic stirring bar. The flask is flushed with argon, after which 10.65 g (0.07 mol) of (S)-(-)-perillyl alcohol (Note 1) followed by 350 mL of dichloromethane (Note 2) is injected through the septum into the flask. The solution is stirred and 37.3 mL (0.147 mol) of triisobutylaluminum (Note 3) is added from the dropping funnel over a period of 2 min at room temperature (Note 4). After the mixture is stirred at room temperature for 20 min, 7.3 mL (0.091 mol) of diiodomethane (Note 5) is added dropwise with a syringe over a 10-min period. The mixture is stirred at room temperature for 4 hr, and poured into 400 mL of ice-cold 8% aqueous sodium hydroxide. The organic layer is separated, and the aqueous layer is extracted twice with 100-mL portions of

dichloromethane. The combined extracts are dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator at ca. 20 mm. The residual oil is distilled under reduced pressure to give 10.64-11.13 g (92-96%) of 1-hydroxymethyl-4-(1-methylcyclopropyl)-1-cyclohexene as a colorless liquid, bp 132-134°C (24 mm) (Notes 6 and 7).

2. Notes

1. (S)-(-)-Perillyl alcohol is available from Aldrich Chemical Company, Inc.

2. Reagent-grade dichloromethane was dried and stored over Linde type 4 A molecular sieves.

3. Neat triisobutylaluminum of 97.6% purity was supplied in a metal cylinder from Toyo Stauffer Chemical Company, Ltd. (Japan). This reagent is also available from Aldrich Chemical Company, Inc. Since neat triisobutylaluminum is pyrophoric and reacts violently with oxygen and water, the used syringe should be immediately washed with hexane.

4. During this operation an exothermic reaction took place.

5. Diiodomethane, available from Tokyo Kasei Kogyo Company, Ltd. (Japan), was used without any purification.

6. The spectral properties of the product are as follows: ^1H NMR (CDCl_3 , 500 MHz) δ : 0.22 and 0.26 (m, 4 H, cyclopropyl C-H), 0.80-0.92, 1.24-1.30, and 1.36-1.47 (m, 3 H, cyclohexenyl C-H), 0.93 (s, 3 H, CH_3), 1.77-1.83 (m, 1 H, cyclohexenyl $=\text{C}-\text{C}-\text{H}$), 1.91-2.16 (m, 4 H, OH and cyclohexenyl $=\text{C}-\text{C}-\text{H}$), 3.99 (br t, 2 H, CH_2-O), 5.69 (br s, 1 H, $=\text{C}-\text{C}-\text{H}$); IR (liquid film) cm^{-1} : 3330, 2830-2960, 1423-1460, 1390, 1010, 1000.

7. Gas chromatographic analysis of the trimethylsilyl ether using a 25-m PEG-HT capillary column at 100°C indicated a purity of 93% (retention time: 11.2 min). Under the present conditions, neither the starting perillyl alcohol nor the isomeric monocyclopropanation product (1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]heptane) were detected. Dicyclopropanation products amounted to less than 5%.

Discussion

This procedure illustrates a new method for selective cyclopropanation of unsaturated alcohols not obtainable with ordinary cyclopropanation reactions.² The selectivity in this trialkylaluminum-promoted cyclopropanation is complementary to that obtained in the Simmons-Smith reaction and its modifications,³ which give facile hydroxyl-assisted cyclopropanations with perillyl alcohol to afford 1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]heptane predominantly. A similar tendency was observed in the case of geraniol. Thus, cyclopropanation with the $i\text{-Bu}_3\text{Al}/\text{CH}_2\text{I}_2$ system takes place almost exclusively at the C(6)-C(7) olefinic site far from the hydroxyl group of geraniol, and the C(2)-C(3) olefinic bond is left intact.²

The present cyclopropanation using trialkylaluminum-methylene iodide may proceed via dialkyl(iodomethyl)aluminum as an active intermediate,⁴ which can be also generated by the reaction of dialkylaluminum iodide with diazomethane.⁵ In addition, reaction of diiodomethane with triisobutylaluminum (each 1 equiv) afforded nearly 1 equiv of isobutyl iodide as a product, suggesting the formation of diisobutyl(iodomethyl)aluminum in the solution.²

The combined use of a wide variety of trialkylaluminum compounds and alkylidene iodide serves as a highly convenient and versatile method for cyclopropanation of simple olefins under mild conditions.² For example, treatment of 1-dodecene with $\text{CH}_2\text{I}_2/\text{R}_3\text{Al}$ ($\text{R} = \text{Me}, \text{Et}, i\text{-Bu}$) in dichloromethane at room temperature for 3-8 hr gave decylcyclopropane in 96-98% yields.

1. Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

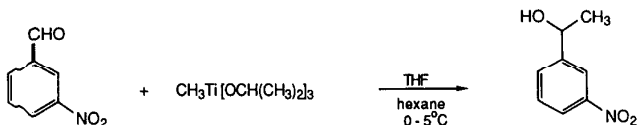
(S)-(-)-Perillyl alcohol: 1-Cyclohexene-1-methanol, 4-(1-methylethenyl)- (8,9); (536-59-4)

1-Hydroxymethyl-4-(1-methylcyclopropyl)-1-cyclohexene: 1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)- (11); (98678-72-9)

3'-NITRO-1-PHENYLETHANOL BY ADDITION OF METHYLTRIISOPROPOXY-

TITANIUM TO m-NITROBENZALDEHYDE

(Benzenemethanol, α -methyl-3-nitro-)



Submitted by René Imwinkelried and Dieter Seebach.¹

Checked by Cheryl A. Martin and K. Barry Sharpless.

1. Procedure

A dry, 500-mL, three-necked flask equipped with a pressure-equalizing 100-mL dropping funnel, argon inlet, and magnetic stirrer is evacuated and flushed with argon (3 cycles). The flask is charged with 16.0 mL (57.7 mmol) of tetraisopropyl orthotitanate (Note 1) via a plastic syringe and hypodermic needle and 2.1 mL (19.2 mmol) of titanium tetrachloride is added over 5 min, with gentle cooling of the flask in an ice-water bath, to give a viscous oil (Note 2). After the addition of 70 mL of tetrahydrofuran (Note 3), the clear solution is stirred at room temperature for 30 min. The dropping funnel is charged with 62 mL (77 mmol, 1.24 M in hexane) of methyllithium (Note 4), which is added to the cooled (ice bath) tetrahydrofuran solution over a period of 25-30 min. During the addition the resulting suspension changes from orange to bright yellow. After the mixture has stirred at ice-bath temperature for 1 hr, a solution of 10.6 g (70 mmol) 3-nitrobenzaldehyde (Note 5) in 60 mL of tetrahydrofuran (Note 3) is added from the dropping funnel within 20-

25 min at the same temperature. The mixture is stirred at 0-5°C for 1 hr and then 60 mL of 2 N hydrochloric acid is added. The organic phase is separated in a separatory funnel and the aqueous phase is extracted with three 150-mL portions of diethyl ether. The combined organic phases are washed with 100 mL of saturated sodium bicarbonate solution and 100 mL of saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. After filtration the solution is concentrated on a rotary evaporator and dried at 0.1 mm for 1 hr. The residue, 11.0-11.1 g (94-95%) of an orange-brown viscous oil, sometimes solidifies on standing (mp 55-60°C); the purity of the crude product is at least 95% (estimated by ^1H NMR). The product can be purified by short-path distillation at 120-125°C (0.15 mm) to give 9.9-10.4 g (85-89%) of a yellow oil, which solidifies on standing at room temperature or at -30°C in a freezer, mp 60.5-62.0°C (lit.² mp 62°C) (Note 6).

2. Notes

1. Commercial tetraisopropyl orthotitanate $[\text{Ti}(\text{O-i-Pr})_4]$ (Dynamit Nobel) and titanium tetrachloride (Fluka pract.) can be used without further purification. The checkers obtained $\text{Ti}(\text{O-i-Pr})_4$ from Aldrich Chemical Company, Inc. and titanium tetrachloride from Fluka. Distillation of $\text{Ti}(\text{O-i-Pr})_4$ did not improve the results.

2. If the mixture is overcooled, the resulting chlorotriisopropoxytitanium partially solidifies.

3. Tetrahydrofuran was distilled from potassium/benzophenone immediately before use.

4. The methyllithium solution was obtained from Metallgesellschaft, Frankfurt. The checkers used methyllithium (Aldrich Chemical Company, Inc.), salt free 1.4 M in ethyl ether, with no significant difference observed in the reaction.

5. 3-Nitrobenzaldehyde is Fluka purum, used without further purification. The checkers obtained it from Aldrich Chemical Company, Inc.

6. The product obtained after distillation can be recrystallized from benzene/petroleum ether (3:2, v:v) to give pale yellow crystals (91-95% from distilled product) with a melting point of 61-63°C. Attempts by the checkers to crystallize the crude reaction mixture were unsuccessful. ^1H NMR (CDCl_3) δ : 1.54 (d, 3 H, $J = 6.5$, CH_3), 2.3 (br, 1 H, OH), 5.00 (q, $J = 6.5$, O-C-H), 7.5-7.7 (m, 2 H, arom. H), 8.0-8.25 (m, 2 H, arom. H); IR (KBr), cm^{-1} : 3260 (br, m), 2990 (m), 1580 (m), 1525 (s), 1340 (s), 1205 (m), 1170 (m), 810 (m), 740 (m), 690 (m).

3. Discussion

The addition of nucleophilic organometallic compounds (usually RLi or RMgX) to a carbonyl group - a key step in numerous syntheses - is not always straightforward. The addition reaction is complicated by the fact that aldehydes, ketones, and esters are not well differentiated, that other electrophilic functional groups such as cyano, nitro, halo, trialkylstannyl may interfere, and that proton abstraction or one electron-transfer processes rather than addition occur. For example, the addition of methyllithium or methylmagnesium iodide to 3-nitrobenzaldehyde under the same conditions used with $\text{CH}_3\text{Ti}(\text{OCH}(\text{CH}_3)_2)_3$ (this procedure) leads to a complex mixture of products with formation of only 10-30% of 3'-nitro-1-phenylethanol.³ In many cases

these complications can be remedied by using derivatives of titanium and zirconium, compounds which have become increasingly important in organic syntheses during the past decade. Several review articles discuss different aspects.³

The nucleophilic titanium and zirconium reagents are readily available by simple transmetallation of the organolithium or Grignard reagents with $(RO)_3TiCl$, $(RO)_3ZrCl$, or $(R_2N)_3TiX$. The trialkoxychloro compounds are prepared by mixing the inexpensive, industrially available, titanates, $Ti(OR)_4$, or zirconates, $Zr(OR)_4$, with the appropriate amount of $TiCl_4$ or $ZrCl_4$. In contrast to compounds of most other heavy metals, few toxic effects of $Ti(OR)_4$ and $Zr(OR)_4$ are known, partly because they are very rapidly hydrolyzed by water and the resulting oxide-hydrates are insoluble (TiO_2 is a white pigment). Some of the reagents, $RTi(OR')_3$, can be isolated without difficulty. Thus, $CH_3Ti(O-i-Pr)_3$ can be obtained as a bright yellow oil which distills without decomposition at $50^\circ C/0.001$ mm.⁴

The organo-titanium and -zirconium compounds, for the most part generated in situ, react highly selectively with carbonyl compounds. For example, $CH_3Ti(O-i-Pr)_3$ reacts five orders of magnitude faster with benzaldehyde than with acetophenone at room temperature.⁵ Reagents of the type $RTi(O-i-Pr)_3$ add smoothly to nitro- (see this procedure), iodo-, or cyano-substituted benzaldehydes, and the reactions may be performed in chlorinated solvents or in acetonitrile (for some examples see Table). The zirconium analogues have particularly low basicity and add in high yield to α - and β -tetralones.⁶ The inclusion of chiral OR^* groups gives enantioselective reagents (up to $\geq 98\%$ ee).^{7,8,9} Allylic $(RO)_3Ti$ -derivatives react diastereoselectively only at the more highly substituted carbon atom with aldehydes and even with unsymmetrical

ketones.^{8,9,10} Titanates can be used as mild catalysts for the transesterification of compounds containing acid- or base-labile functional groups.¹¹

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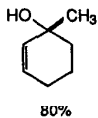
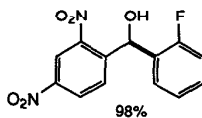
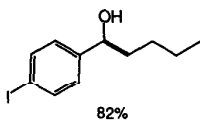
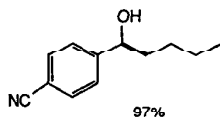
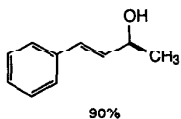
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

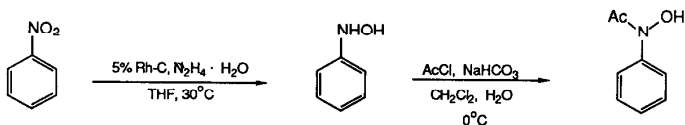
- 3'-Nitro-1-phenylethanol: Benzyl alcohol, α -methyl-m-nitro- (8);
Benzenemethanol, α -methyl-3-nitro- (9); (5400-78-2)
m-Nitrobenzaldehyde: Benzaldehyde, m-nitro- (8); Benzaldehyde, 3-nitro- (9);
(99-61-6)
Methyltriisopropoxytitanium: Titanium, triisopropoxymethyl- (8); Titanium,
methyltris(2-propanolato)-, (T-4)- (9); (18006-13-8)
Tetraisopropyl orthotitanate: Isopropyl alcohol, titanium (4+) salt (8);
2-Propanol, titanium (4+) salt (9); (546-68-9)

TABLE

SOME PRODUCTS OF ORGANOTITANIUM TRIISOPROPOXIDES [RTi(OiPr)₃] WITH FUNCTIONALIZED CARBONYL COMPOUNDS.³ THE BONDS MADE DURING THE REACTION ARE DRAWN BOLD.



**N-ACETYL-N-PHENYLHYDROXYLAMINE VIA CATALYTIC TRANSFER HYDROGENATION
OF NITROBENZENE USING HYDRAZINE AND RHODIUM ON CARBON
(Acetamide, N-hydroxy-N-phenyl-)**



Submitted by P. W. Oxley, B. M. Adger, M. J. Sasse, and M. A. Forth.¹

Checked by Soo Y. Ko and K. Barry Sharpless.

1. Procedure

Caution! Nitrobenzene and hydrazine are both toxic. Phenylhydroxylamine and N-acetyl-N-phenylhydroxylamine are both suspected carcinogens.

A. N-Phenylhydroxylamine. Wet, 5% rhodium on carbon (1.1 g) (Note 1), tetrahydrofuran (200 mL) (Note 2) and nitrobenzene (41.0 g) (Note 3) are introduced into a 500-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer and condenser. The mixture is cooled to 15°C and hydrazine hydrate (17.0 g) (Note 4) is introduced into the reaction mixture from a pressure-equalized addition funnel over 30 min. The temperature of the mixture is maintained at 25–30°C throughout the addition by means of an ice-water bath. After the mixture is stirred for a further 2 hr at 25–30°C, the reaction is complete (Note 5). The mixture is filtered and the catalyst washed with a little tetrahydrofuran. The solution is used immediately in the acylation step (Note 6).

B. *N-Acetyl-N-phenylhydroxylamine*. To the *N*-phenylhydroxylamine solution in a 1000-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer and thermometer is added a slurry of sodium bicarbonate (42 g) in water (40 mL). The mixture is cooled to -4°C in an ice-salt bath before acetyl chloride (26.0 g) (Note 7) is introduced into the well-stirred mixture over 1 hr (Note 8) while the temperature is maintained below 0°C . Stirring is then continued for 30 min before a solution of sodium hydroxide (20.0 g) in water (200 mL) is added keeping the temperature below 20°C . The aqueous phase is separated, the tetrahydrofuran phase is diluted with an equal volume of petroleum ether, the aqueous phase is separated again, and the organic phase is extracted with aqueous 10% sodium hydroxide solution (2 x 50 mL). The combined aqueous phases are washed with methylene chloride (200 mL) and then neutralized with concentrated hydrochloric acid (cooling employed). The mixture is extracted with methylene chloride (3 x 100 mL) and the extracts are combined, dried over magnesium sulfate, filtered and concentrated at reduced pressure (about one fifth volume) (Note 9). After the solution is cooled to 40°C , 100 mL of petroleum ether (bp $60-80^{\circ}\text{C}$) is added. The mixture is stirred at 10°C for 30 min before filtering and washing with additional petroleum ether. The material is dried at room temperature to afford 39.3-40.1 g (79-80%) of *N*-acetyl-*N*-phenylhydroxylamine as a white crystalline solid, mp $66-67^{\circ}\text{C}$ [lit.² mp $67-67.5^{\circ}\text{C}$] (Note 10).

2. Notes

1. The 5% rhodium on carbon used was purchased dry from Engelhard Industries Ltd. The checkers purchased it from Aldrich Chemical Company, Inc. The catalyst is used wet (40-50% water) to reduce the risk of fire when the solvent is added.

2. Tetrahydrofuran was from a bulk supply purchased from Blagden Campbell. The checkers obtained it from EM Science. The solvent was tested for peroxides prior to use.

3. Nitrobenzene was supplied by BDH Chemicals Ltd., and was used as received. The checkers obtained it from Aldrich Chemical Company, Inc. Nitrobenzene should be handled only with gloves and in an efficient fume hood.

4. Hydrazine hydrate was purchased from FBC Industrial Chemicals and was used as supplied. The checkers obtained it from Aldrich Chemical Company, Inc. Hydrazine is a severe poison and should be handled only with gloves in an efficient fume hood.

5. An HPLC system was used to monitor the reduction and to determine the end of the reaction. The HPLC monitoring was not employed by the checker. However, TLC indicated that the reduction was almost complete after stirring for 2 hr at 25-30°C. If only a slight excess (1.03 equiv) of hydrazine is employed the reaction is generally complete in 2 hr and excessive over-reduction cannot occur.

The HPLC system consisted of a Waters C₁₈ μ -Bondapak column, a mobile phase consisting of 15% acetonitrile, 85% 0.05 M aqueous ammonium acetate using a flow rate of 2 mL/min, and a UV wavelength detector for 235 nm. The relative response factors of nitrobenzene and aniline were 1.75 and 0.66, respectively.

6. N-Phenylhydroxylamine, mp 83.5-85°C, can be isolated at this stage in 75-85% yields if desired, but it should be borne in mind that N-phenylhydroxylamine is not very stable. The isolation can be carried out by adding an equal volume of methylene chloride to the tetrahydrofuran solution which is then dried over magnesium sulfate and concentrated to low volume under reduced pressure. Addition of a little petroleum ether precipitates N-phenylhydroxylamine which is then filtered and washed with petroleum ether.

7. Acetyl chloride was obtained from Hoechst and was used as supplied. The checkers obtained it from Fluka Chemical Corporation. The quantity of acetyl chloride used is 1.05 equiv based on the HPLC yield. (The checkers simply used the amount specified.) Acetyl chloride should be handled only with gloves in an efficient fume hood.

8. No vigorous, exothermic reaction is seen during the addition of acetyl chloride, but the addition should be slow because of the heterogeneous nature of the reaction and the need to destroy efficiently hydrogen chloride as it is formed. The product, like N-phenylhydroxylamine, is sensitive to acid and undergoes the Bamberger rearrangement.³

9. Excessive heating causes decomposition of the product. This method also affords an easily handled crystalline solid of good purity.

10. The following analytical data have been obtained: ¹H NMR (CDCl₃, 100 MHz) δ : 2.11 (s, 3 H acetylmethyl); 7.40 (m, 5 H, aromatics); 8.90 (broad, 0.6 H, NOH); IR (Nujol) cm⁻¹: 3140, 2930, 2860, 1630, 1595, 1460, 1380. Anal. Calcd. for C₈H₉NO₂: C, 63.56; H, 6.00; N, 9.27. Found C, 63.48; H, 5.99; N, 9.21. Non-aqueous titration (Bu₄NOH), 98.3%.

3. Discussion

This preparation illustrates a convenient reduction of nitrobenzene under catalytic transfer hydrogenation conditions to give N-phenylhydroxylamine in high yield and demonstrates a mono-acylation method to afford the N-acetyl derivative in high yield. Some work has been done in this area by Johnstone, et al.⁴ A number of other reductive methods described in the literature were tried,^{5,6,7} but these were not as good as the procedure described here. Phenylhydroxylamine is thermally unstable, can undergo a Bamberger

rearrangement,³ and deteriorates on storage, so its isolation is undesirable. The material was therefore converted directly, without isolation, to its more stable N acetyl derivative. Other acylation methods led to mixtures of mono and diacylated products.

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Appendix

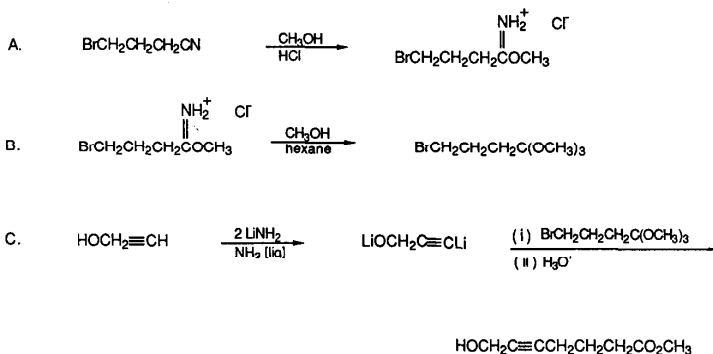
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-Phenylhydroxylamine: Hydroxylamine, N-phenyl- (8); Benzenamine, N-hydroxy- (9); (100-65-2)

N-Acetyl-N-phenylhydroxylamine: Acetohydroxamic acid, N-phenyl- (8); Acetamide, N-hydroxy]-N-phenyl- (9); (1795-83-1)

METHYL 7-HYDROXYHEPT-5-YNATE

(5-Heptynoic acid, 7-hydroxy-, methyl ester)



Submitted by Guy Casy,¹ John W. Patterson,² and Richard J. K. Taylor.¹

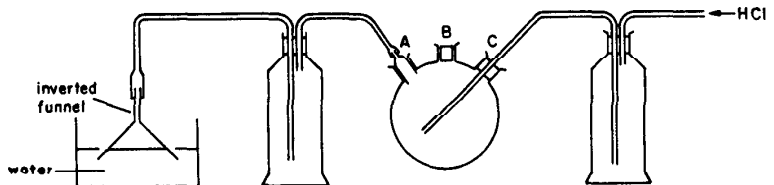
Checked by Friedhelm Balkenhohl and E. Winterfeldt.

1. Procedure

A. *Methyl 4-bromo-1-butanimidate hydrochloride*. A 500-mL, three-necked, round-bottomed flask is connected via neck A to a hydrogen chloride water trap using the arrangement shown in Figure 1. A stream of nitrogen (Note 1) is introduced via neck C; the flask is flame-dried and allowed to cool. The stopper is removed from neck B and the flask is charged with 29.6 g (0.20 mol) of 4-bromobutanenitrile (Note 2), 200 mL of dry ether (Note 3) and 7.7 g (0.24 mol; 1.2 equiv based on 1.0 equiv of 4-bromobutanenitrile) of dry methanol (Note 3). The stopper is replaced, and the weight of the flask and its

contents are recorded. The flask and its contents are cooled to -5°C by immersion in an ice-salt bath, the nitrogen source is removed, and the gas inlet tube is connected to the cylinder of hydrogen chloride. The cylinder tap is cautiously opened, and hydrogen chloride is allowed to bubble through the reaction mixture at a steady but controlled rate until 18.2 g (0.50 mol; 2.5 equiv based on 1.0 equiv of 4-bromobutanenitrile) has been absorbed (Note 4). A stopper is placed in each neck of the flask and a strip of Parafilm is bound around the edge of each ground-glass connection to ensure an airtight seal.

Figure 1



The flask is stored at 5°C (refrigerator) for 4-5 days (Note 5), after which time a copious precipitate of the title compound is obtained. The mixture is filtered with suction through a dry 100-mm sintered glass funnel. After all of the product is collected, a large inverted funnel connected to a nitrogen source is positioned about 15 cm above the sintered funnel to provide a blanket of dry, inert gas (Note 6). The product is washed thoroughly with

several portions of dry ether, totaling 500 mL, and then dried to constant weight over solid potassium hydroxide in a desiccator evacuated at 12-20 mm (water aspirator). There is obtained 39.0 g (90%) (Note 7) of methyl 4-bromo-1-butanimidate hydrochloride as fine white crystals, mp 95-97°C (Note 8).

B. Trimethyl ortho-4-bromobutanoate. A 1-L, two-necked, round-bottomed flask containing an efficient magnetic stirring bar is purged with nitrogen (Note 1) introduced via a pressure-equalizing glass bubbler (Note 9). The flask is charged with 38.9 g (0.18 mol) of methyl 4-bromo-1-butanimidate hydrochloride, 450 mL of dry hexane (Note 3) and 17.3 g (0.54 mol) of dry methanol (Note 3). A stopper is placed in one neck of the flask; the glass bubbler is removed from the other neck and immediately replaced with a gas outlet adapter to which is attached a balloon filled with nitrogen (Note 10). Finally, a strip of Parafilm is bound around the edge of each ground-glass connection to ensure an airtight seal. The reaction mixture is stirred at room temperature for 48 hr, then filtered with suction to remove the precipitated ammonium chloride. The filter cake is washed with two 30-mL portions of dry hexane, and the filtrate and washings are concentrated under reduced pressure (water aspirator) at 30-40°C by rotary evaporation to leave a slightly turbid, colorless liquid, to which is added 0.25 g of anhydrous potassium carbonate. This material is distilled under reduced pressure to afford 36.4-36.7 g (89-90%) (Note 11) of trimethyl ortho-4-bromobutanoate as a colorless oil, bp 65°C (0.5 mm) (Note 12).

C. Methyl 7-hydroxyhept-5-ynoate. A 2-L, three-necked, round-bottomed flask equipped with a dry ice condenser and a mechanical stirring rod is charged with 750 mL of anhydrous ammonia, via a gas-inlet tube, at -33°C (Note 13) under nitrogen (Notes 1 and 14). The gas-inlet tube is removed, and about 0.1 g of lithium wire (Note 2) is added in small portions until a permanent

blue color is obtained. Ferric nitrate (0.1 g) is added to discharge the blue color, and after the solution is stirred for 5 min, 4.24 g (0.611 mol; 2.5 equiv based on 1.0 equiv of propargyl alcohol) of lithium wire is added in small portions. After the addition is complete the flask is fitted with a 100-mL pressure-equalizing and serum-capped dropping funnel. Stirring is continued for 20 min to obtain a grey suspension of lithium amide, to which is added dropwise a solution of 13.7 g (0.245 mol; 1.5 equiv based on 1.0 equiv of trimethyl ortho-4-bromobutanoate) of redistilled propargyl alcohol (Note 2) in 15 mL of dry ether (Note 3). After the solution is stirred for 20 min, a solution of 36.4 g (0.160 mol) of trimethyl ortho-4-bromobutanoate in 40 mL of dry ether is added dropwise. Stirring is continued for 3 hr, the reaction vessel is opened to the atmosphere, and its contents are allowed to warm to room temperature over 16-18 hr. The mixture is heated at 50°C on a water bath under a stream of nitrogen to remove any remaining ammonia. This furnishes a grey solid, which is cooled to 0°C, and 5% sulfuric acid is added in 100-mL portions until a pH of 1 is obtained (Note 15). The resulting suspension is stirred at room temperature for 30 min, and extracted with three 200-mL portions of ether. The combined organic extracts are washed with 200 mL of saturated sodium bicarbonate, dried over magnesium sulfate, and filtered. The filtrate is concentrated under reduced pressure (water aspirator) at 30-40°C by rotary evaporation, to leave 19.1 g (77%) of an essentially pure amber oil (Note 16). This material can be distilled under reduced pressure to afford 16.8 g (67%) (Note 17) of methyl 7-hydroxyhept-5-ynoate as a colorless oil, bp 100°C (0.05 mm) (Notes 18 and 19).

2. Notes

1. Oxygen-free nitrogen, dried by passage through activated molecular sieves, was used.

2. 4-Bromobutanenitrile was obtained from Lancaster Synthesis Ltd. Alternatively it can be prepared from 1,3-dibromopropane and potassium cyanide using the procedure of Derrick and Henry.³ Lithium wire (3.2 mm diameter, containing ca. 0.01% sodium) and propargyl alcohol were obtained from the Aldrich Chemical Company, Inc. The latter was dried with potassium carbonate and then distilled prior to use.

3. Diethyl ether and hexane were freshly distilled from blue solutions obtained with sodium and benzophenone. Methanol was distilled from magnesium and iodine. The use of high purity solvents (e.g., Mallinckrodt AR anhydrous ether, Nanograde hexane and AR methanol) as received gave only small reductions in yield.

4. To monitor uptake of hydrogen chloride the flask and its contents are periodically weighed. Typically, the process is complete within 5 min.

5. The progress of the reaction can be monitored by tilting the flask slightly to expose clear supernatant liquor. The flask is left in this position overnight, and if no further crystallization is apparent, the product may be isolated.

6. Alternatively a dry nitrogen glove box can be employed.

7. In several smaller scale experiments (0.07-0.14 mol of 4-bromobutanenitrile) yields in the range 83-93% were achieved.

8. The product has the following spectroscopic properties: IR (Nujol) cm^{-1} : 1650, 1405, 1215, 875; ^1H NMR (TFA-d) δ : 2.08-2.64 (m, 2 H), 3.04 (t, 2 H, $J = 7$), 3.48 (t, 2 H, $J = 6$), 4.32 (s, 3 H), 9.52 (br s, 2 H); ^{13}C NMR (TFA-d) δ : 28.53, 30.82, 33.41, 60.77, 183.65.

9. The glassware was dried overnight at 150°C and assembled hot under nitrogen.

10. This arrangement is preferable to a continuous flow of nitrogen; otherwise the quantity of methanol in situ may be critically diminished.

11. In several smaller scale experiments (0.05-0.12 mol of methyl 4-bromo-1-butanimidate hydrochloride) yields in the range 90-93% were achieved.

12. The product has the following spectroscopic properties: IR (neat) cm^{-1} : 2840, 1740, 1070; ^1H NMR (CDCl_3) δ : 1.77-2.03 (m, 4 H), 3.23 (s, 9 H), 3.33-3.60 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 26.54, 29.00, 33.87, 49.37, 115.31.

13. To minimize evaporation of liquid ammonia, a temperature of $-33 \pm 5^\circ\text{C}$ was maintained until the workup by means of a dry ice-acetone cooling bath. In addition, the dry ice condenser was continually charged with a saturated dry ice-acetone mixture.

14. The apparatus is maintained under a slight positive nitrogen pressure until the work up. If this precaution is not taken, atmospheric moisture is drawn into the apparatus (see Note 19).

15. A total volume of 500-600 mL of 5% sulfuric acid is normally required.

16. This material is essentially pure as indicated by TLC and ^1H NMR spectroscopic analyses, and by CH microanalysis. (Anal. Calcd for $\text{C}_8\text{H}_{12}\text{O}_3$: C, 61.5; H, 7.7. Found: C, 61.8; H, 7.9.)

17. On a smaller scale (0.109 mol of trimethyl ortho 4 bromobutanoate) in which a magnetic stirring bar was used to agitate the reaction mixture, a distilled yield of 71% (81% before distillation) was achieved.

18. The submitters report bp 120°C (0.06 mm). The product has the following spectroscopic properties: IR (neat) cm^{-1} : 3420, 1735, 1015; ^1H NMR (CDCl_3) δ : 1.63-2.63 (m, 6 H), 3.24 (s, 1 H), 3.67 (s, 3 H), 4.12-4.30 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 18.02, 23.54, 32.64, 50.73, 51.43, 79.32, 84.31, 173.60.

19. If moisture is drawn into the apparatus, this can diminish the quantity of the dilithio derivative of propargyl alcohol. If any O-lithio monoanion is present during the addition of trimethyl ortho-4-bromobutanoate, a quantity of the O-alkylated derivative, methyl 4-(2-propynyloxy)butanoate will be produced. The latter exhibits the following ^1H NMR (CDCl_3) spectrum: δ : 1.61-2.58 (m, 5 H), 3.52 (t, 2 H, $J = 5.5$), 3.65 (s, 3 H), 4.09 (d, 2 H, $J = 2.5$).

3. Discussion

Methyl 7-hydroxyhept-5-ynoate is an important precursor to alkylating agents that are used to introduce the complete prostaglandin α -side chain.^{4,5} It is normally prepared from propargyl alcohol using a six-step sequence originally introduced by Corey and Sachdev⁶ with subsequent modifications.⁷⁻¹¹ Alternative routes to methyl 7-hydroxyhept-5-ynoate have also been reported^{12,13} but appear less efficient than the one described here. The present route arose from the observation that whereas alkylations of propargyl alcohol-derived anions with 4-halobutanoates were unsuccessful,^{13,14} the use of trimethyl ortho-4-bromobutanoate gave efficient alkylation.¹⁴ Related reactions using orthoester protecting groups have been reported recently¹⁵ and the preparation of such compounds from nitriles using the Pinner reaction, as described herein, is well established.¹⁶

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 7-hydroxyhept-5-ynoate: 5-Heptynoic acid, 7-hydroxy-, methyl ester
(9), (50781-91-4)

4-Bromobutanenitrile: Butyronitrile, 4-bromo- (8); Butanenitrile, 4-bromo-
(9); (5332-06-9)

Trimethyl ortho-4-bromobutanoate: Butane, 4-bromo-, 1,1,1-trimethoxy- (9);
(55444-67-2)

4-METHOXY-3-PENTEN-2-ONE
(3-Penten-2-one, 4-methoxy-)



Submitted by George A. Kraus, Michael E. Krolski and James Sy.¹

Checked by Yun Gao and K. Barry Sharpless.

1. Procedure

4-Methoxy-3-penten-2-one. A flame-dried, 250-mL, one-necked flask equipped with a condenser and drying tube is charged with 2,4-pentanedione (Note 1) (25.0 g, 250 mmol), trimethyl orthoformate (Note 2) (26.53 g, 250 mmol), p-toluenesulfonic acid (0.54 g, 2.8 mmol) and methanol (Note 3) (62 mL). The flask is placed in an oil bath and heated at 55°C for 5 hr. The solution is cooled and concentrated under reduced pressure. Fifty milliliters of CCl₄ is added and the solution is again concentrated under reduced pressure. The crude product is distilled via a short path condenser and collected in a flask cooled in an ice bath (Note 4). The product distills at 43-47°C (4 mm) at an oil bath temperature of 60°C (Note 5). The yield of pure product is 17.3-18.8 g (61-66%) (Note 6).

2. Notes

1. 2,4-Pentanedione was obtained from Aldrich Chemical Company, Inc. Its purity was greater than 99% and was used without purification.
2. The trimethyl orthoformate used in this experiment was obtained from Aldrich Chemical Company, Inc. Its purity was listed as 98% and was used without purification.
3. Methanol was obtained from Fisher Scientific. It was anhydrous grade methanol.
4. The checkers used a dry ice-acetone cooling bath.
5. Use of higher temperature ($>65^{\circ}\text{C}$) results in a low yield.
6. The spectral properties of 4-methoxy-3-penten-1-one are as follows:
IR (neat) cm^{-1} : 1674, 1590, 1165, 922. NMR (CDCl_3) δ : 2.15 (s, 3 H), 2.28 (s, 3 H), 3.64 (s, 3 H), 5.41 (s, 1 H).

3. Discussion

4-Methoxy-3-penten-2-one has been prepared by Awang using methanol and sulfuric acid.² He also determined the stereochemistry by NMR solvent shift data and observation of nuclear Overhauser effects. Our preparation is a convenient, one pot procedure. The title compound is useful for effecting the overall γ -alkylation of enones³ and has been used in a synthesis of prostaglandins.⁴

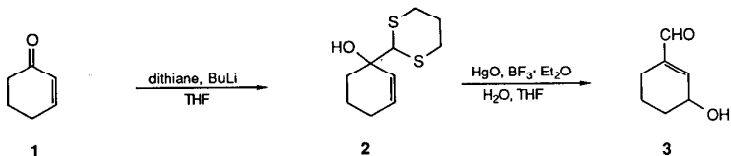
1. Department of Chemistry, Iowa State University, Ames, IA 50011.
2. Awang, D. V. C. *Can. J. Chem.* **1971**, *49*, 2672.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

4-Methoxy-3-penten-2-one: 3-Penten-2-one, 4-methoxy- (8,9); (2845-83-2)
2,4-Pentanedione (8,9); (123-54-6)

3-HYDROXY-1-CYCLOHEXENE-1-CARBOXALDEHYDE
(1-Cyclohexene-1-carboxaldehyde, 3-hydroxy-)



Submitted by H. L. Rigby, M. Neveu, D. Pauley, B. C. Ranu, and T. Hudlicky.¹
 Checked by Denis R. St. Laurent and Leo A. Paquette.

1. Procedure

A. 1-(1,3-Dithian-2-yl)-2-cyclohexen-1-ol (2). To a suspension of 1,3-dithiane (Note 1) (12 g, 0.1 mol) in dry tetrahydrofuran (100 mL) (Note 2) at -78°C is added butyllithium (40 mL, 2.5 M, 0.1 mol). The reaction is stirred for 2 hr. Initially the dithiane dissolves, followed by precipitation of the lithio salt. After 2 hr, 2-cyclohexen-1-one (9.6 g, 0.1 mol) (Note 3) in dry tetrahydrofuran (20 mL) is added dropwise. After about half of the cyclohexenone is added, the mixture becomes homogeneous. After the addition is complete, the reaction is stirred for an additional 30 min at -78°C and then stored for 18 hr at 0°C . The solution is concentrated to one-fourth volume under reduced pressure. Water (100 mL) is added and the mixture is extracted with ether (3 x 50 mL). The extract is dried over sodium sulfate and evaporated to give an oil which is vacuum distilled to give 14.0-14.7 g (65-68%) of the protected aldehyde 2, bp $149-153^\circ\text{C}$ (0.8-1.0 mm) (Note 4).

B. *3-Hydroxy-1-cyclohexene-1-carboxaldehyde* (3). The hydroxy thioacetal 2 (5.5 g, 0.025 mol) in 25 mL of tetrahydrofuran is added dropwise to a mechanically-stirred suspension of red mercuric oxide (11 g, 0.051 mol) (Note 5) and boron trifluoride etherate (7.2 g, 0.051 mol) (Note 6) in refluxing 15% aqueous tetrahydrofuran (50 mL). After the addition is complete, the mixture is stirred (Note 7) at reflux for an additional 2 hr. Another 5.5 g of red mercuric oxide is added and the reaction is stirred at reflux for 1 hr. The reaction is cooled to room temperature and ether (150 mL) is added followed by 50 mL of brine. The mixture is filtered and the residue washed with ether (3 x 50 mL). The organic layer is separated and washed with saturated sodium bicarbonate solution (2 x 50 mL) and brine (1 x 50 mL). The organic layer is dried over sodium sulfate and the solvent evaporated to leave a residual oil. This oil is purified by medium pressure liquid chromatography (silica gel, elution with 40% ethyl acetate in hexane) to give 1.5-1.6 g (47-50%) of the aldehyde 3, bp 125°C (0.075 mm) (Kugelrohr) (Note 8).

2. Notes

1. Dithiane was obtained from Aldrich Chemical Company, Inc. and was used without purification.

2. Tetrahydrofuran was distilled under nitrogen from potassium and benzophenone.

3. 2-Cyclohexen-1-one was obtained from Aldrich Chemical Company, Inc. and used as received.

4. The submitters report bp 157°C (1 mm). The spectral properties of **2** are as follows: IR (neat) cm^{-1} : 3450 (br), 3030, 2940, 2900 (sh), 2830, 1645 (w), 1425, 1280, 1185, 1085, 985; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.57-2.08 (m, 8 H), 2.40 (s, 1 H), 2.74-2.90 (m, 4 H), 4.17 (s, 1 H), 5.68 (d, 1 H, $J = 10.05$), 5.85-5.91 (m, 1 H); ^{13}C NMR (CDCl_3 , 20 MHz) δ : 18.53, 24.98, 25.75, 30.35, 30.54, 33.03, 59.54, 71.75, 129.43, 132.18; MS: M^+ 198, 120, 119 (base), 97, 91, (no M^+ peak).

5. Mercuric oxide (red) was purchased from Aldrich Chemical Company, Inc. and used without purification.

6. Boron trifluoride etherate was distilled from calcium hydride at aspirator pressure.

7. Mechanical stirring was found to be essential and in some cases addition of sea sand to the reaction mixture reduced clogging of the reagents and led to higher yields.


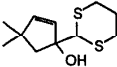
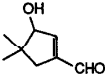
8. The submitters report bp 70°C (10^{-4} mm). The spectral properties of **3** are as follows: IR (neat) cm^{-1} : 3400 (br), 2950, 2870, 2720, 1675, 1435, 1305, 1180, 1135, 1070, 1045, 995, 965, 925; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.47-1.54 (m, 2 H), 1.71-1.79 (m, 1 H), 1.90 1.98 (m, 1 H), 2.06 (s, 2 H), 3.49 (br s, 1 H), 4.37 (br s, 1 H), 6.63 (s 1 H), 9.34 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 18.54, 20.94, 31.35, 65.84, 77.43, 141.63, 150.88, 194.49; MS: M^+ 97, (base), 79, 69, 55, 41.

3. Discussion

Preparation of a compound such as 3 is useful where extensive functionalization of a cyclic enone is required. In addition to 3, 4,4-dimethyl-3-hydroxy-1-cyclopentene-1-carboxaldehyde was prepared using the same procedure from 4,4-dimethyl-2-cyclopenten-1-one.² The Table below gives yields and physical properties for this compound which has been used as a starting material in the syntheses of coriolin and pentalenic acid.³

TABLE

PREPARATION OF 4,4-DIMETHYL-3-HYDROXY-1-CYCLOPENTENE-1-CARBOXALDEHYDE

Enone	Dithiane	Hydroxy Aldehyde
	 79% bp 130-132°C/0.05 mm	 55%

1. Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061.
2. Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273.
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Appendix

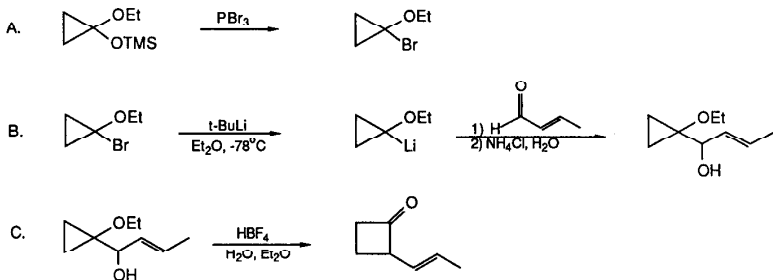
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 3-Hydroxy-1-cyclohexene-1-carboxaldehyde: 1-Cyclohexene-1-carboxaldehyde,
3-hydroxy- (10); (67252-14-6)
- 1-(1,3-Dithian-2-yl)-2-cyclohexen-1-ol: 2-Cyclohexen-1-ol,
1-(1,3-dithian-2-yl)- (9); (53178-46-4)
- Cyclohexenone: 2-Cyclohexen-1-one (8,9); (930-68-7)
- 4,4-Dimethyl-2-cyclopenten-1-one: 2-Cyclopenten-1-one, 4,4-dimethyl- (8,9);
(22748-16-9)

SYNTHESIS OF CYCLOBUTANONES VIA 1-BROMO-1-ETHOXYCYCLOPROPANE:

(E)-2-(1-PROPENYL)CYCLOBUTANONE

(Cyclobutanone, Z-(1-propenyl)-, (E))



Submitted by Scott A. Miller and Robert C. Gadwood.¹

Checked by Jeffrey A. McKinney and Leo A. Paquette.

1. Procedure

A. *1-Bromo-1-ethoxycyclopropane.*² A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a calcium sulfate drying tube is charged with 84.1 g (0.483 mol) of 1-ethoxy-1-trimethylsilyloxycyclopropane.³ Phosphorus tribromide (35.6 mL, 103 g, 0.379 mol) (Note 1) is added at room temperature with brisk stirring, followed by a catalytic amount (0.5 ml) of 48% aqueous hydrobromic acid (Note 2). The resulting clear, pale yellow solution is stirred for 6 hr (Note 3). After the stirring bar is removed, the reaction mixture is distilled by Kugelrohr apparatus at aspirator vacuum (10

mm) from 25°C to 70°C to afford crude 1-bromo-1-ethoxycyclopropane (Notes 4 and 5). The crude product is dissolved in 300 mL of pentane in a 1-L Erlenmeyer flask and the resulting solution is chilled to -20°C in a dry ice-ethanol: water (30:70) bath. While the temperature of the solution is maintained below 25°C, 300 mL of saturated, aqueous sodium carbonate is carefully added (Note 6). The layers are carefully shaken and separated, and the aqueous phase is extracted with 100-mL of pentane. The organic layer is dried over magnesium sulfate, filtered, and most of the pentane is removed by distillation through a 15-cm Vigreux column at atmospheric pressure. The residue is transferred to a smaller distillation flask and distilled through the same column under aspirator vacuum to afford 47.0-57.6 g (59-72%) of 1-bromo-1-ethoxycyclopropane as a colorless liquid (bp 35-43°C, 10 mm) (Notes 7 and 8).

Caution! Because of the relatively large amount of pyrophoric tert-butyllithium involved, the following preparation should be performed in a hood behind a safety shield.

B. *(E)*-1-Ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane. A 1-L, three-necked flask is equipped with a gas inlet adapter, a septum, a 250-mL graduated addition funnel capped with a septum, and a magnetic stirring bar (Note 9). The flask is charged with 500 mL of anhydrous diethyl ether (Note 10) and cooled to -78°C under nitrogen atmosphere. The addition funnel is charged with 177 mL (19.2 g, 0.30 mol) of tert-butyllithium (Note 11), transferred from the reagent bottle via a stainless steel cannula under positive nitrogen pressure. The tert-butyllithium is added dropwise to the stirred diethyl ether over approximately 20 min while the cooling bath is maintained at -78°C. After the addition is complete, 26.4 g, (0.16 mol) of freshly prepared 1-bromo-1-ethoxycyclopropane is added to the reaction over

about 5 min by syringe. The resulting cloudy, colorless or light yellow reaction mixture is stirred for 20-25 min, and a solution of 7.0 g (0.10 mol) of crotonaldehyde (Note 12) in 50 mL of anhydrous diethyl ether (chilled to -78°C) is added via a stainless steel cannula under positive nitrogen pressure. The reaction mixture is stirred at -78°C for an additional 10 min, warmed to 0°C in an ice bath, and carefully quenched with 100 mL of saturated, aqueous ammonium chloride. The layers are shaken and separated and the aqueous phase is extracted with 100 mL of diethyl ether. The combined organic layers are dried over magnesium sulfate and filtered. After the crude adduct is concentrated on a rotary evaporator, it is filtered through a 10-cm pad of silica gel (Note 13) in a sintered-glass funnel with 10% ethyl acetate in hexane. After concentrating again on a rotary evaporator, the crude adduct is obtained as a pale yellow oil (14.2-15.6 g) (Note 14). This material is not further purified, but is used directly in the next reaction.

C. *(E)*-2-(1-Propenyl)cyclobutanone. To a 1-L, round-bottomed flask equipped with a magnetic stirring bar is added 15.3 g (0.098 mol) of *(E)*-1-ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane, 500 mL of reagent grade diethyl ether and 6.6 mL (4.3 g, 0.049 mol) of 48% aqueous fluoboric acid (Note 15). After the reaction mixture is stirred for 15 min at room temperature, it is quenched with 60 mL (0.06 mol) of 1 M aqueous sodium carbonate. The layers are carefully shaken and separated, and the organic phase is washed with three 125-mL portions of water (Note 16). The combined aqueous layers are extracted with 100 mL of diethyl ether and the organic phase is dried over magnesium sulfate and filtered. The filtrate is concentrated on a rotary evaporator without external heating and the residue is distilled through a 10-cm Vigreux column under aspirator vacuum. The product, 7.2-8.3 g (66-75% yield from crotonaldehyde), is obtained as a colorless oil, bp $61-65^{\circ}\text{C}$ (10 mm) (Note 17).

2. Notes

1. Phosphorus tribromide was obtained from the Aldrich Chemical Company, Inc. and used without further purification.

2. The addition of a catalytic amount of hydrobromic acid was frequently found to be necessary to initiate the reaction, especially if the phosphorus tribromide is of high purity. Upon addition of the hydrobromic acid, the reaction warms noticeably.

3. The course of the reaction is most conveniently followed by ^1H NMR analysis of a drop of the reaction mixture in carbon tetrachloride. The downfield quartet of the starting ketal (3.52 ppm) is replaced by a clean quartet at 3.62 ppm from the product. The checkers have found by this technique that reaction is complete in much less than 6 hr.

4. The crude product thus obtained also contains bromotrimethylsilane and hydrobromic acid.

5. *Caution!* After distillation the Kugelrohr apparatus should first be cooled and then carefully vented to an atmosphere of nitrogen since traces of elemental phosphorus may be present in the pot residue and may ignite if exposed to air while still hot.

6. This step neutralizes the hydrobromic acid and bromotrimethylsilane present in the product. Therefore, addition of the aqueous sodium carbonate solution is exothermic and causes vigorous carbon dioxide evolution. Cooling at this stage helps prevent hydrolysis of the product.

7. A low boiling, silicon-containing fraction is also collected below 37°C (28 mm). The presence of a singlet at 0.10 ppm in the ^1H NMR of the product indicates contamination by this low boiling fraction. Small amounts of this impurity do not seem to interfere in subsequent reactions of the 1-bromo-1-ethoxycyclopropane.

8. 1-Bromo-1-ethoxycyclopropane is relatively unstable at room temperature, but can be stored for several months at -20°C with only slight decomposition. Spectral data for 1-bromo-1-ethoxycyclopropane are as follows: IR (neat) cm^{-1} : 3100 (w), 2985 (s), 2935 (m), 2885 (m), 1445 (m), 1300 (s), 1160 (s), 1060 (s), 795 (s); ^1H NMR (CCl_4) δ : 1.17 (m, 7 H), 3.53 (q, 2 H, $J = 8$); MS (15 eV), m/e 164/166 (M^+), 136/138 (base), 85, 57.

9. The glassware was dried in an oven overnight at 110°C and assembled while hot under nitrogen flow.

10. Diethyl ether was dried by distillation from sodium metal/benzophenone.

11. *Caution! tert-Butyllithium is extremely pyrophoric and should only be handled on a large scale by experienced personnel.* tert-Butyllithium was obtained from the Aldrich Chemical Company, Inc. as a 1.7 M solution in pentane. In general, this material was used as received without titration.

12. Crotonaldehyde was obtained from The Matheson Company, Inc., and is also available (99+% grade) from the Aldrich Chemical Company, Inc.

13. Merck Silica Gel 60 (230-400 mesh) was obtained from the Aldrich Chemical Company, Inc. Filtration through silica gel removes residual inorganic salts (mostly lithium chloride) which may interfere in the subsequent rearrangement step.

14. Spectral data for (E)-1-ethoxy-1-(1-hydroxy-2-butenyl)cyclopropane are as follows: ^1H NMR (CDCl_3) δ : 0.68 (m, 4 H), 1.12 (t, 3 H, $J = 6$), 1.64 (d, 3 H, $J = 5$), 2.46 (s, 1 H), 3.54 (m, 2 H), 4.15 (d, 1 H, $J = 6$), 5.52 (m, 2 H). Occasionally, a minor impurity is formed as a result of the addition of tert-butyllithium to crotonaldehyde (singlet at 0.89 ppm in the ^1H NMR). This side reaction occurs because of the presence of unreacted tert-butyllithium and is best avoided by using the indicated ratio of tert-butyllithium to 1-bromo-1-ethoxycyclopropane. The checkers were unable to remove this impurity by fractional distillation.

15. Fluoboric acid was obtained as a 48 wt % aqueous solution from the Aldrich Chemical Company, Inc. Based upon its density, this solution was calculated to be approximately 7.4 M in HBF_4 . The checkers used 5.4 mL (0.049 mol) of 60% fluoboric acid.

16. Washing with water helps to remove the ethanol generated in the course of the rearrangement. For higher boiling cyclobutanones, where the ethanol can easily be removed during distillation, this step is unnecessary.

17. Spectral data for (E)-2-(1-propenyl)cyclobutanone are as follows: IR (CCl_4) cm^{-1} : 2960 (s), 1780 (s), 1660 (w), 1450 (m); ^1H NMR (CCl_4) δ : 1.62 (m, 3 H), 2.17 (m, 2 H), 2.88 (m, 2 H), 3.73 (m, 1 H), 5.37 (m, 2 H). The product was contaminated by an alcoholic impurity to the extent of 6-11%.

3. Discussion

Cyclobutanones have attained a position of considerable synthetic importance in recent years. In addition to being important synthetic targets themselves, they serve as useful precursors of five-,⁴ six-,⁵ and eight-membered⁶ rings, as well as of a variety of highly functionalized acyclic fragments.^{7,8}

In general, cyclobutanones are synthesized by either ketene cycloadditions or by ring expansions of cyclopropyl precursors. For the synthesis of simple α -substituted monocyclic cyclobutanones, the latter method is usually employed, and a variety of approaches have been used to prepare the required cyclopropyl intermediates.

Vinylcyclopropanols have been prepared by the addition of alkenyl Grignard reagents to a variety of cyclopropanone equivalents.⁹ Upon treatment with acid, the vinylcyclopropanols rearrange to α -substituted cyclobutanones. Alternatively, a variety of α -heteroatom-substituted cyclopropyllithium reagents have been developed. These react with aldehydes and ketones to afford cyclopropylcarbinols which also rearrange to cyclobutanones under acid catalysis.^{8,10,11} Lastly, vinylcyclopropanols and cyclopropylcarbinols have been prepared by the cyclopropanation of enol silyl ethers and allylic alcohols.¹²

There are several advantages to the procedure described here for the synthesis of α -substituted cyclobutanones. The preparation of 1-bromo-1-ethoxycyclopropane is convenient and can be accomplished in good overall yield in only two steps from commercially available ethyl 3-chloropropionate. Metalation of 1-bromo-1-ethoxycyclopropane is rapid and reproducible on a large scale and (1-ethoxy)cyclopropyllithium adds cleanly to a wide variety of

ketones and aldehydes. Finally, rearrangement of the cyclopropylcarbinol adducts occurs smoothly and in high yield.

The preparation of 1-bromo-1-ethoxycyclopropane is based on a literature report of the synthesis of 1-bromo-1-methoxycyclopropane from 1-methoxy-1-trimethylsiloxycyclopropane using phosphorus tribromide in pyridine.¹³ In our hands, reaction of 1-ethoxy-1-trimethylsiloxycyclopropane under these conditions afforded none of the bromide.

The title cyclobutanone has been prepared previously by the addition of (1-phenylthio)cyclopropyllithium to crotonaldehyde followed by rearrangement with anhydrous stannic chloride in methylene chloride.¹¹ However, in our experience, the procedure described here is much more convenient and reproducible on a large scale.

As shown in the Table, a wide variety of α -substituted cyclobutanones have been prepared by the general method described here.¹⁴ The time required for rearrangement of the intermediate cyclopropylcarbinols varies from less than 5 min for entry 2 to 48 hr for entry 10. With most enones and enals, only 1,2-addition is observed, but in two cases (entries 3 and 4), a significant amount of the 1,4-adduct was also produced. The increased 1,4-addition seen in entry 3 apparently occurs because of steric factors, whereas that seen in entry 4 presumably occurs because of chelation of the organolithium to the benzyl ether oxygen.

1. Department of Chemistry, Northwestern University, Evanston, IL 60201.
2. Gadwood, R. C. *Tetrahedron Lett.* **1984**, *25*, 5851; Gadwood, R. C.; Rubino, M. R.; Nagarajan, S. C.; Michel, S. T. *J. Org. Chem.* **1985**, *50*, 3255.
3. Salaün, J.; Marguerite, J. *Org. Synth.* **1985**, *63*, 147.
4. Gadwood, R. C. *J. Org. Chem.* **1983**, *48*, 2098, and references therein.







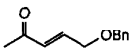
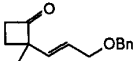
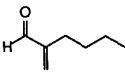
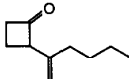


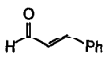
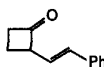
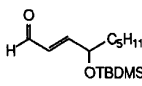
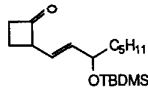


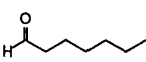
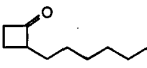
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14. Entries 2, 9, and 10 of Table I have been previously reported.² Entry 1 was carried out by Amy J. DeWinter. Entry 3 was carried out by Scott A. Miller. Entry 4 was carried out by Mark R. Rubino. Entries 5-8 were carried out by Ishwar M. Mallick.

TABLE

CYCLOBUTANONE SYNTHESIS VIA 1-BROMO-1-ETHOXYCYCLOPROPANE

Entry	Ketone/aldehyde	Cyclobutanone	Yield (%)
1			97
2			86
3			40
4			30
5			65
6			71
7			79
8			74
9			81
10			81

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Bromo-1-ethoxycyclopropane: Cyclopropane, 1-bromo-1-ethoxy- (11);
(95631-62-2)

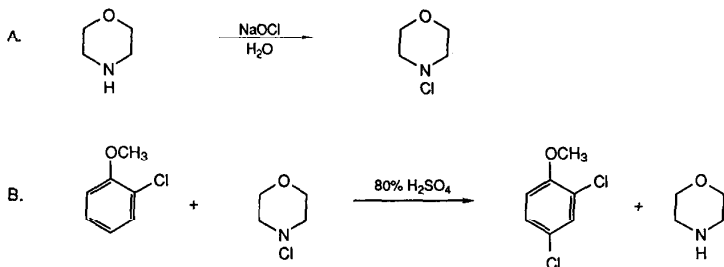
(E)-2-(1-Propenyl)cyclobutanone: Cyclobutanone, 2-(1-propenyl)-, (E)- (10);
(63049-06-9)

1-Ethoxy-1-trimethylsiloxycyclopropane: Silane, [(1-ethoxycyclopropyl)oxy]-
trimethyl- (8,9); (27374-25-0)

4-CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS:

2,4-DICHLOROMETHOXYBENZENE

(Benzene, 2,4-dichloro-1-methoxy-)



Submitted by John R. Lindsay Smith, Linda C. McKeer, and Jonathan M. Taylor.¹

Checked by Yasushi Morita and Ryoji Noyori.

1. Procedure

A. *N*-Chloromorpholine. A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, mechanical stirrer and thermometer is charged with 250 mL of 1.5 M sodium hypochlorite solution (Note 1). The solution is stirred and the temperature is maintained below 10°C while 30 mL (0.34 mol) of morpholine (Note 2) is added-dropwise. The resulting mixture is stirred for 5 min before the *N*-chloromorpholine is extracted with four 50-mL portions of diethyl ether. The combined ether extracts are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator (Note 3). The concentrate is distilled at reduced pressure (Note 4) to afford 35.5-36.5 g (86-88%) of *N*-chloromorpholine, bp 63-64°C (36-38 mm) (Note 5).

B. *2,4-Dichloromethoxybenzene*. A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel, mechanical stirrer and thermometer is charged with 250 mL of 80% (v/v) sulfuric acid (Note 6) and cooled in an ice bath before 16 g (0.11 mol) of 2-chloromethoxybenzene (Note 7) is added with stirring. The stirring and cooling are maintained while 14.5 g (0.12 mol) of N-chloromorpholine is added dropwise (Note 8). The cooling bath is removed and stirring is continued for 1 hr. The reaction mixture is carefully poured into a mixture of 150 mL of distilled water and 100 g of crushed ice in a 1-L flask cooled at 0°C (Note 9). The aromatic products are extracted with a 100-mL portion, followed by four 50-mL portions, of diethyl ether. The combined ether extracts are washed with 100 mL of water containing 0.5 g of potassium iodide, 2 g of sodium thiosulfate and 2 mL of acetic acid (Note 10) followed by 50 mL of 8% (w/v) aqueous sodium hydroxide (Note 11), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure to afford 15.2-16.0 g (77-81%) of 2,4-dichloromethoxybenzene, bp 110-111°C (10 mm) [lit.² bp 125°C (10 mm), 233°C (740 mm)]. The product after distillation is 98.9-99.2% pure, the major impurities being 2,6-dichloromethoxybenzene (0.4-0.5%) and 2,4,6-trichloromethoxybenzene (0.4-0.6%) (Notes 12 and 13). If the above purity is insufficient, it can be improved to >99.9% by recrystallization (Notes 14 and 15).

2. Notes

1. Solutions of sodium hypochlorite of different concentration can be used with a corresponding change in the volume. The submitters purchased sodium hypochlorite solution from BDH Chemicals Ltd., England. The material

initially contains 10-14% available chlorine, but it deteriorates on standing over a period of weeks. The checkers used the material (chlorine content 9-14%) purchased from Nakarai Chemicals, Ltd., Japan.

2. Gold Label grade morpholine (99+%) was obtained from Aldrich Chemical Company, Inc., and used as supplied.

3. Since N-chloromorpholine has a low boiling-point, the water bath temperature should not exceed 30°C.

4. It is recommended that a water or oil bath, or a hot air blower, be used for this distillation to avoid the risk of local overheating.

5. N-Chloromorpholine should be handled with extreme care at all times. On standing at room temperature it slowly decomposes, forming crystals of morpholine hydrochloride. However, it can be stored for several weeks at -18°C. Vigorous decomposition of N-chloromorpholine has been reported when it is distilled at atmospheric pressure.³ The checkers removed the small quantity of salt contamination by filtration through a glass filter and used the pure liquid in the subsequent chlorination reaction.

6. Trifluoroacetic acid, 100 mL, obtainable from Aldrich Chemical Company, Inc., can be used instead of aqueous sulfuric acid (see Discussion, part 3).

7. 2-Chloromethoxybenzene was obtained from Aldrich Chemical Company, Inc., and was distilled prior to use, bp 195-196°C or 112°C (41 mm).

8. Since the dissolution of N-chloromorpholine in sulfuric acid (or trifluoroacetic acid) and the subsequent reaction between protonated N-chloromorpholine and 2-chloromethoxybenzene are both exothermic processes, the addition of the chloroamine should be carried out at such a rate as to keep the reaction temperature below 5°C. The checkers found that a reaction run at 8°C gave product of only 93% purity.

9. If the reaction is carried out in trifluoroacetic acid, the product mixture is made basic by adding it cautiously, with cooling and stirring, to a cold solution of 50 g of sodium hydroxide in 150 mL of distilled water. The aromatic products are then extracted with diethyl ether as described in the main text.

10. If trifluoroacetic acid is used, more acetic acid may be required to ensure that the aqueous layer is acidic. Should any iodine remain, more sodium thiosulfate should be added until all of the iodine has been converted to iodide.

11. The aqueous layer should remain basic after washing with sodium hydroxide. If it is still acidic, this wash should be repeated.

12. If trifluoroacetic acid is used as solvent, the purity is 98-99% and the impurities are mainly 2,6-dichloro- and 2,4,6-trichloromethoxybenzene.

13. The purity of the product can be determined by gas-liquid chromatography using a column packed with 10% (w/w) Carbowax 20 M on Celite (80-100 mesh) at 195°C, nitrogen carrier gas flow rate 35 mL min⁻¹.

14. Eighteen grams of 2,4-dichloromethoxybenzene is dissolved in 20 mL of light petroleum ether and chilled to -18°C. Crystallization can be induced by either scratching or seeding. The mixture is kept at -18°C for 1 hr to maximize the yield before the crystals are filtered with a Buchner funnel and washed with 10 mL of chilled light petroleum ether. The crystals are sucked dry, and then dried in a vacuum desiccator. The recrystallized yield of 2,4-dichloromethoxybenzene is 12.8 g (55-58% overall), mp 25.5-26.5°C, lit.² mp 28°C.

15. The product had the following spectral properties. IR (neat) cm⁻¹: 1483, 1288, 1254, 1055, 700; ¹H NMR (CCl₄, 60 MHz) δ: 3.77 (s, 3 H, OCH₃), 6.70 (d, 1 H, J = 9.0, H₆), 7.05 (dd, 1 H, J = 9.0 and 2.5, H₅), 7.27 (d, 1 H,

$J = 2.5, H_3$); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ : 56.2 (q), 112.7 (d), 123.3 (s), 125.6 (s), 127.5 (d), 129.9 (d), 153.9 (s); mass spectrum (70 eV) m/e (rel. intensity): 178 ($M^+ + 2$, 56), 176 (M^+ , 100), 163 (41), 161 (58), 135 (23), 133 (43); mass spectrum calcd for $C_7H_6OCl_2$ (M^+): 175.9797, found: 175.9809.

3. Discussion

Chlorine or hypochlorous acid has been used traditionally for the chlorination of aromatic compounds and, when required, the reactivity of these reagents can be increased with a Lewis or protic acid, respectively.⁴ However, these reactions are rarely selective for one monochlorinated product (site-selective⁵) and, furthermore, with some substrates di- and polychlorination can also occur. The increasing need for isomerically pure chloroaromatics in recent years has led to the development of more selective chlorinating agents, particularly for electron-rich aromatic compounds (e.g., phenol).⁶ In this respect the submitters have found that *N*-chlorodialkylamines in strongly acidic solution are efficient and very selective mono-chlorinating agents for aromatic compounds containing a π -donor ($+M$) substituent.⁷ Thus, normally the addition of the *N*-chloroamine to an equimolar quantity of the substrate in acid leads rapidly and almost exclusively to the para-chlorinated product (Table I). Although, for reasons of economy most of the reactions have been studied on a small scale (<1 g of substrate), the submitters have had no difficulty in scaling up the chlorinations to use 20 g of substrate. The two acidic media that have been used with success are trifluoroacetic acid and aqueous sulfuric acid [commonly 80% (v/v) sulfuric acid]. The advantages of the former are that the reactions are homogeneous, can if necessary be carried out at low temperature (below

0°C) and can be monitored readily by ^1H NMR spectroscopy. However, trifluoroacetic acid is relatively expensive and is highly toxic (the reactions must be carried out in a well-ventilated hood). In situations where these disadvantages outweigh the advantages, aqueous sulfuric acid is generally a cheap and less toxic alternative. The fact that the reactions in aqueous sulfuric acid are not homogeneous is not a serious problem. Thus, with efficient stirring the chlorinations occur rapidly; furthermore, solid substrates can be added as solutions in diethyl ether (e.g., with N-chloromorpholine, phenol gave 93% of 4-chloro- and 7% of 2-chlorophenol, and 2-methylphenol gave 95% of 4-chloro- and 5% of 6-chloro-2-methylphenol). The major disadvantage in the use of aqueous sulfuric acid arises with the most reactive substrates (e.g., some phenols) from competing aromatic sulfonation. However, this can be reduced to a minor side-reaction by keeping the reaction mixture cold (below 8°C the 80% sulfuric acid reaction mixtures will begin to freeze) and by minimizing the time between the addition of the substrate and of the chloroamine to the aqueous sulfuric acid.

The structure of the N-chlorodialkylamine markedly affects its reactivity and to a lesser extent its selectivity (Table II). Thus with 2-chloromethoxybenzene as substrate, N-chloromorpholine is approximately 17,000 times more reactive than N-chloropiperidine and yet it is only slightly less selective for para-chlorination of methoxybenzene. For most substrates the shorter reaction times (less chance of other side reactions) of the more reactive N-chloroamines more than compensates for any small decrease in selectivity.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,4-Dichloromethoxybenzene: Anisole, 2,4-dichloro- (8); Benzene,

2,4-dichloro-1-methoxy- (9); (553-82-2)

N-Chloromorpholine: Morpholine, 4-chloro- (8,9); (23328-69-0)

Morpholine (8,9); (110-91-8)

2-Chloromethoxybenzene: Anisole, o-chloro- (8); Benzene, 1-chloro-2-methoxy- (9); (766-51-8)

TABLE I
YIELD AND PRODUCT DISTRIBUTIONS FROM THE CHLORINATION
OF AROMATIC COMPOUNDS IN TRIFLUOROACETIC ACID^a


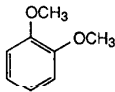

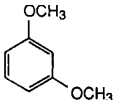
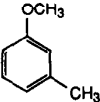
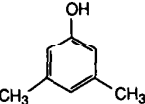
Substrate	Chlorinating Agent	Yield ^b (%)	Product	Product Distribution (%)
<chem>C6H5OMe</chem>	NCP ^c	97	2-chloromethoxybenzene	1
			4-chloromethoxybenzene	99
<chem>C6H5OH</chem>	NCP	98	2-chlorophenol	3
			4-chlorophenol	97
	NCP	84	6-chloro-2-methylphenol	1.5
			4-chloro-2-methylphenol	98.5
	NCTA ^d	80	4-chloro-1,2-dimethoxybenzene	100
	NCP	89	4-chloro-3-methylphenol	98
			4,6-dichloro-3-methylphenol	2
	NCP	79	4-chloro-1,3-dimethoxybenzene	91
			4,6-dichloro-1,3-dimethoxybenzene	9

TABLE I (contd.)

	NCP	85	4-chloro-3-methylmethoxy- benzene	100
	NCTA ^e	95	4-chloro-3,5-dimethylphenol 4,6-dichloro-3,5-dimethyl- phenol	96 4

^aEquimolar quantities of substrate and N-chloro compound.

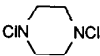

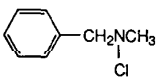
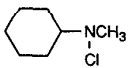

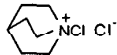
^bYield of products isolated from reaction, based on N-chloro compound.

^cNCP = N-chloropiperidine.

^dNCTA = N-chlorotriethylammonium chloride.⁸

^eTwo-fold excess of substrate, reaction temperature -17°C.

TABLE II
RELATIVE REACTIVITY AND SELECTIVITY OF
N-CHLORINATED AMINES IN TRIFLUOROACETIC ACID

N-Chloro Compound	Reactivity Relative to NCP ^a	Ratio of 4- to 2-Chlorination ^b
	160 000	6.0
	17 000	20
	200	48
	9	66
	1	99
	0.2	500

^aDetermined from chlorination of 2-chloromethoxybenzene.

NCP = N-chloropiperidine.

^bFrom the chlorination of methoxybenzene.

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- 2423R* Palladium Catalyzed Coupling of Vinyl Triflates with Organostannanes: 1-Vinyl-4-tert-Butylcyclohexene and 1-(4-tert-Butylcyclohex-1-enyl)propenone
G. T. Crisp, W. J. Scott, and J. K. Stille, Department of Chemistry, Colorado State University, Ft. Collins, CO 80523
- 2443* 4,13-Diaza-18-crown-6
V. J. Gatto, S. R. Miller, and G. W. Gokel, Department of Chemistry, University of Miami, Coral Gables, FL 33124
- 2451R Ester Homologation via Ynolate Anions: Methyl 3-Cyclohexenylacetate
C. J. Kowalski and S. Sakdarat, Synthetic Chemistry Department, Smith Kline and French Laboratories, P.O. Box 7929, Philadelphia, PA 19101
- 2456R* Intramolecular Cyclization of cis-cis-1,5-Cyclooctadiene Using Hypervalent Iodine: Synthesis of 8-Cyclo[3.3.0]octa-2,6-dione
R. M. Moriarty, M. P. Duncan, O. Prakash, and R. K. Vaid, Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60680
- 2463 Allyltributyltin
N. G. Halligan and L. C. Blaszcak, Department of Chemical, Infectious Disease and Cancer Research, Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN 46285
- 2465* Cyclopentadiene Annulation via the Skattebøl Rearrangement: (1R)-9,9-Dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-diene
L. A. Paquette and M. L. McLaughlin, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2468R* Synthesis of (Phenylthio)nitromethane
A. G. M. Barrett, D. Dhanak, G. G. Graboski, and S. J. Taylor, Department of Chemistry, Northwestern University, Evanston, IL 60201
- 2469* Yeast Reduction of 2,2-Dimethylcyclohexane-1,3-dione: (S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone
K. Mori and H. Mori, Department of Agricultural Chemistry, The University of Tokyo, Bunkyo-Ku, Tokyo 113, Japan
- 2472 Propargylation of Alkyl Halides: Synthesis of (E)-6,10-Dimethyl-6,9-undecadien-1-yne and (E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol
J. Hooz, J. Cabezas, S. Musmanni, and J. Calzada, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2
- 2473* Preparation of 4-(S)-Phenylmethyl-2-Oxazolidinone
J. R. Gage and D. A. Evans, Department of Chemistry, Harvard University, Cambridge, MA 02138
- 2474* A Highly Diastereoselective Aldol Reaction Using a Chiral Oxazolidinone Auxiliary
J. R. Gage and D. A. Evans, Department of Chemistry, Harvard University, Cambridge, MA 02138

- 2476* Immonium Ion Based Diels-Alder Reactions: N-Benzyl-2-azanorbornene
P. A. Grieco and S. D. Larsen, Department of Chemistry, Indiana University, Bloomington, IN 47405
- 2477* Transesterification of Methyl Esters of Aromatic and α,β -Unsaturated Acids with Bulky Alcohols: (-)-Menthyl Cinnamate and (-) Menthyl Nicotinate
O. Meth-Cohn, Research and Development Director, Sterling Organics Ltd., Edgefield Avenue, Fawdon, Newcastle-on-tyne NE3 3TT, United Kingdom
- 2478* p-tert-Butylcalix[4]arene
C. D. Gutsche and M. Iqbal, Department of Chemistry, Washington University, St. Louis, MO 63130
- 2479 p-tert-Butylcalix[6]arene
C. D. Gutsche, B. Dhawan, and M. Leonis, Department of Chemistry, Washington University, St. Louis, MO 63130
- 2480* p-tert-Butylcalix[8]arene
J. H. Munch and C. D. Gutsche, Department of Chemistry, Washington University, St. Louis, MO 63130
- 2481* Synthesis of 2-(Phenylsulfonyl)-1,3-Cyclohexadiene
J. E. Backvall, S. K. Juntunen, and O. S. Andell, Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden
- 2482* Directed Homogeneous Hydrogenation: Anti-Methyl 3-Hydroxy-2-methylpentanoate
J. M. Brown, P. L. Evans, and A. P. James, University of Oxford, The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, England
- 2483 A General Synthesis of Cyclobutanones from Olefins and Tertiary Amides: 3-Hexylcyclobutanone
C. Schmit, J. B. Falmagne, J. Escudero, H. Vanlierde and L. Ghosez, Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, Place L. Pasteur 1, B-1348, Louvain-La-Neuve, Belgium
- 2484 Synthesis of Racemic cis-4,5-Dihydro-4,5-dimethyl-3-methylene-2(3H)-furanone
S. E. Drewes, R. F. A. Hoole, and S. D. Freese, Department of Chemistry, University of Natal, Pietermaritzburg 3200, South Africa
- 2486 6-Iodo-9-(β -D-ribofuranosyl)purine
V. Nair, Department of Chemistry, The University of Iowa, Iowa City, IA 52242
- 2488* Allylic Acetoxylation of Cycloalkenes
A. Heumann, B. Akermarck, S. Hanson, and T. Rein, Université d'Aix Marseille, Faculté de St.-Jérôme, IPSOI F 13397 Marseille Cedex 13, France

- 2490 3-Butylcyclobutenone
R. L. Danheiser, S. Savariar, and D. D. Cha, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139
- 2491 L-Valinol, By LiAlH_4 Reduction
G. A. Smith, G. Hart, S. Chemburkar, K. Rein, T. V. Anklekar, A. L. Smith, and R. E. Gawley, Department of Chemistry, P.O. Box 249118, University of Miami, Coral Gables, FL 33124
- 2494 Nucleophilic Hydroxymethylation of Carbonyl Compounds: 1-(Hydroxymethyl)cyclohexanol
K. Tamao, N. Ishida, Y. Ito, and M. Kumada, Department of Synthetic Chemistry, Kyoto University, Sakyo-Ku, Kyoto 606, Japan
- 2495 Alkylidenation of Ester Carbonyl Groups: (2E,4Z)-4-Ethoxy-2,4-Decadiene
K. Takai, Y. Kataoka, T. Okazoe, K. Oshima, and K. Utimoto, Department of Industrial Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606, Japan
- 2497 Rearrangement of 4-Aryl-4-hydroxy-2,3-dialkoxycyclobutenediones to Annulated Hydroquinones and Quinones: 5,6-Diethoxybenzofuran-4,7-dione
S. T. Perri, P. Rice, and H. W. Moore, Department of Chemistry, University of California, Irvine, CA 92717
- 2498 Synthesis of Alkyl Propanoates by Haloform Reaction of Trichloro Ketones: Preparation of Ethyl 3,3-Diethoxypropanoate
L. F. Tietze, E. Voss, and U. Hartfiel, Institut für Organische Chemie, der Georg August Universität, Tammannstrasse 2, D-3400 Göttingen, Federal Republic of Germany

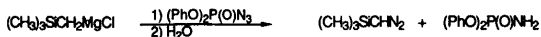
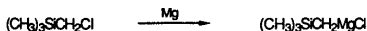
CONTENTS

Takayuki Shioiri, Toyohiko Aoyama, and Shigehiro Mori	1	TRIMETHYLSILYLDIAZOMETHANE
Anthony G. M. Barrett, Dashyant Dhanak, Gregory G. Graboski, and Sven J. Taylor	8	(PHENYLTHIO)NITROMETHANE
M. Mark Midland, Jim I. McLoughlin, and Ralph T. Werley, Jr.	14	PREPARATION AND USE OF LITHIUM ACETYLIDE: 1-METHYL-2-ETHYNYL- endo-3,3-DIMETHYL-2-NORBORNANOL
John A. Soderquist	25	ACETYLTRIMETHYLSILANE
Rick L. Danheiser, Selvaraj Savariar, and Don D. Cha	32	3-BUTYLCYCLOBUTENONE
Jean-Pierre Deprés and Andrew E. Greene	41	VICINAL DICARBOXYLATION OF AN ALKENE: cis-1-METHYLCYCLO- PENTANE-1,2-DICARBOXYLIC ACID
S. H. Zhao, O. Samuel, and H. B. Kagan	49	ENANTIOSELECTIVE OXIDATION OF A SULFIDE: (S)-(-)-METHYL p-TOLYL SULFOXIDE
Kenji Mori and Hideto Mori	56	YEAST REDUCTION OF 2,2-DIMETHYL- CYCLOHEXANE-1,3-DIONE: (S)-(+)-3-HYDROXY-2,2-DIMETHYL- CYCLOHEXANONE
John M. Brown, Phillip L. Evans, and Alun P. James	64	DIRECTED HOMOGENEOUS HYDROGENATION: METHYL anti 3 HYDROXY-2-METHYLPENTANOATE
James R. Gage and David A. Evans	77	(S)-4-(PHENYLMETHYL)-2- OXAZOLIDINONE
James R. Gage and David A. Evans	83	DIASTEREOSELECTIVE ALDOL CONDENSATION USING A CHIRAL OXAZOLIDINONE AUXILIARY: (2S*,3S*) 3-HYDROXY 3-PHENYL 2-METHYLPROPANOIC ACID
Eugene A. Mash, Keith A. Nelson, Shawne Van Deusen, and Susan B. Hemperly	92	1,4-DI-O-ALKYL THREITOLS FROM TARTARIC ACID: 1,4-DI-O-BENZYL-L-THREITOL
Noreen G. Halligan and Larry C. Blaszcak	104	ALLYLTRIBUTYLTIN

A. Heumann, B. Åkermark, S. Hanson, and T. Rein	109	ALLYLIC ACETOXYLATION OF CYCLOALKENES: 2-CYCLOHEPTEN- 1-YL ACETATE
William J. Scott, G. T. Crisp, and J. K. Stille	116	PALLADIUM-CATALYZED COUPLING OF VINYL TRIFLATES WITH ORGANOSTANNANES: 4- <i>tert</i> -BUTYL-1- VINYL CYCLOHEXENE and 1-(4- <i>tert</i> - BUTYL CYCLOHEXEN-1-YL)-2- PROPEN-1-ONE
Norio Miyaura and Akira Suzuki	130	PALLADIUM-CATALYZED REACTION OF 1-ALKENYLBORONATES WITH VINYLIC HALIDES: (1 <i>Z</i> ,3 <i>E</i>)-1-PHENYL-1,3- OCTADIENE
Sandro Cacchi, Enrico Morera, and Giorgio Ortari	138	PALLADIUM-CATALYZED REDUCTION OF VINYL TRIFLUOROMETHANESULFONATES TO ALKENES: CHOLESTA-3,5-DIENE
Jan E. Bäckvall, Seppo K. Juntunen, and Ove S. Andell	148	2-(PHENYLSULFONYL)- 1,3-CYCLOHEXADIENE
Otto Meth-Cohn	155	TRANSESTERIFICATION OF METHYL ESTERS OF AROMATIC AND α,β -UNSATURATED ACIDS WITH BULKY ALCOHOLS: (-)-MENTHYL CINNAMATE AND (-)-MENTHYL NICOTINATE
Jan H. Näsman	162	3-METHYL-2(5H)-FURANONE
Robert M. Moriarty, Michael P. Duncan, Radhe K. Vaid, and Om Prakash	175	INTRAMOLECULAR CYCLIZATION OF <i>cis,cis</i> -1,5-CYCLOOCTADIENE USING HYPERVALENT IODINE: BICYCLO[3.3.0]OCTANE-2,6-DIONE
Larry E. Overman, Mark J. Brown, and Stephen F. McCann	182	(<i>Z</i>)-4-(TRIMETHYLSILYL)-3-BUTEN- 1-OL
Larry E. Overman, Chris J. Flann, and Thomas C. Malone	188	REGIOSELECTIVE SYNTHESIS OF TETRAHYDROPYRIDINES: 1-(4-METHOXYPHENYL)-1,2,5,6- TETRAHYDROPYRIDINE
Richard T. Taylor, Michael W. Pelter, and Leo A. Paquette	198	DOMINO DIELS-ALDER REACTION: 3,3 <i>a</i> ,3 <i>b</i> ,4,6 <i>a</i> ,7 <i>a</i> -HEXAHYDRO- 3,4,7-METHENO-7H-CYCLOPENTA[<i>a</i>]- PENTALENE-7,8-DICARBOXYLIC ACID
Paul A. Grieco and Scott D. Larson	206	IMMONIUM ION-BASED DIELS-ALDER REACTIONS: N-BENZYL-2- AZANORBORNENE

Stephen R. Wilson and Corinne E. Augelli	210	THE CARROLL REARRANGEMENT: 5-DODECEN-2-ONE
Leo A. Paquette and Mark L. McLaughlin	220	CYCLOPENTADIENE ANNULATION VIA THE SKATTEBØL REARRANGEMENT: (1R)-9,9-DIMETHYLTRICYCLO- [6.1.1.0 ^{2,6}]DECA-2,5-DIENE
Vincent J. Gatto, Steven R. Miller, and George W. Gokel	227	4,13-DIAZA-18-CROWN-6
C. D. Gutsche and M. Iqbal	234	p-tert-BUTYLCALIX[4]ARENE
C. D. Gutsche, B. Dhawan, M. Leonis, and D. Stewart	238	p-tert-BUTYLCALIX[6]ARENE
J. H. Munch and C. D. Gutsche	243	p-tert-BUTYLCALIX[8]ARENE
Unchecked Procedures	247	

TRIMETHYLSILYLDIAZOMETHANE
(Silane, (diazomethyl)trimethyl-)



Submitted by Takayuki Shioiri, Toyohiko Aoyama, and Shigehiro Mori.¹

Checked by George Maynard and Leo A. Paquette.

1. Procedure

A. *Trimethylsilylmethylmagnesium chloride*. Magnesium turnings (10.7 g, 0.44 g-atom) are placed in a dry, 300-mL, four-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, 200-mL pressure-equalizing dropping funnel capped with a rubber septum, thermometer, rubber septum, and a reflux condenser connected to an argon flow line. The apparatus is flushed with argon, and an argon atmosphere is maintained throughout the reaction. Anhydrous diethyl ether (40 mL) (Note 1) and 0.1 mL of 1,2-dibromoethane are placed in the reaction flask with a syringe, and the mixture is stirred at room temperature for 15 min. The dropping funnel is charged with a solution of 45.4 g (0.37 mol) of chloromethyltrimethylsilane (Note 2) in 100 mL of anhydrous diethyl ether with a syringe. With stirring, about 10 mL of this solution is added at once. When the reaction has started (Note 3), the remaining solution is added dropwise at such a rate that a gentle reflux

is maintained throughout the addition (addition time about 2 hr). After the exothermic reaction subsides, the resulting solution is stirred at reflux by heating for an additional 1 hr. The reaction mixture is cooled to room temperature, and is used in step B.

B. Trimethylsilyldiazomethane (Note 4). A dry, 1-L, four-necked, round-bottomed flask is equipped with a liquid paraffin-sealed mechanical stirrer (Note 5), rubber septum, 200-mL pressure-equalizing dropping funnel capped with a rubber septum, and a reflux condenser connected to an argon flow line. The apparatus is flushed with argon, and an argon atmosphere is maintained throughout the reaction. A solution of 91.2 g (0.33 mol) of diphenyl phosphorazidate (Note 6) in 350 mL of anhydrous diethyl ether is placed in the flask with a syringe. The rubber septum is quickly replaced by a low-temperature thermometer. The Grignard reagent prepared in step A is transferred to the dropping funnel with a syringe. The flask is cooled with an ice-sodium chloride bath, and the stirring is started. When the internal temperature reaches -10°C , the Grignard reagent is added dropwise at such a rate that the internal temperature is maintained below 0°C (addition time about 1.5 hr) (Note 7). After the addition is complete, the ice-salt bath is replaced with an ice bath and the mixture is stirred for 2 hr, then allowed to stand in the ice bath for 14-16 hr. The reaction mixture is cooled again to -15°C with an ice-sodium chloride bath. With vigorous stirring, 35 mL of cold water is carefully added dropwise at such a rate that the internal temperature is maintained below 0°C (addition time about 1 hr), and the stirring is continued for 0.5 hr (Note 8). The reaction mixture is then filtered by suction using a glass filter. The white solid is thoroughly washed with three 100-mL portions of diethyl ether. The combined filtrate is washed with two 100-mL portions of cold water and dried over anhydrous sodium sulfate. After

the sodium sulfate is removed by filtration, the filtrate is placed in a 1-L, round-bottomed flask equipped with a Teflon coated magnetic stirring bar and a 30-cm Vigreux column (15-mm diameter). With constant stirring by a magnetic stirrer, the solution is slowly concentrated to a volume of about 200 mL by distillation at atmospheric pressure with the bath temperature below 45°C. The concentration time requires about 6 hr (Notes 9 and 10). The remaining deep yellow solution is distilled through the same apparatus under reduced pressure between 100 mm at 0°C (bath temperature) and 15 mm at 40°C (bath temperature) until no more volatile material comes over, and the distillate is collected in a receiver cooled in a dry ice-acetone bath. The distillate is dried again over anhydrous sodium sulfate. The drying agent is removed by filtration, and 100 mL of hexane (Note 11) is added to the filtrate. In a manner similar to that described above, this solution is slowly concentrated by distillation at atmospheric pressure through a 30-cm Vigreux column (15-mm diameter). The color of the distillate gradually becomes yellow. Concentration is continued until the temperature of the vapor reaches 68°C (final oil bath temperature 87°C). The concentration requires about 3 hr (Note 9). Approximately 80-110 mL of the remaining yellow hexane solution contains 220-230 mmol of trimethylsilyldiazomethane (67-70% yield based on diphenyl phosphorazidate) (Notes 12, 13). This hexane solution can be stored without decomposition for periods exceeding 6 months at 0°C with protection from light.

2. Notes

1. Diethyl ether was distilled from lithium aluminum hydride under argon before use.

2. Chloromethyltrimethylsilane, obtained from Petrarch Systems Inc., was purified by distillation at 97°C under atmospheric pressure.

3. If the reaction does not start, the flask is gently heated by a heat gun.

4. *Trimethylsilyldiazomethane is both non-explosive and non-mutagenic.² Therefore, the very careful operations³ used for the preparation of diazomethane are not necessary.*

5. A glass or Teflon stirring rod should be used.

6. Diphenyl phosphorazidate, obtained from either Daiichi Pure Chemicals Co., Ltd. or Aldrich Chemical Company, Inc., was purified by distillation under reduced pressure; bp 134-136°C/0.2 mm. It can be easily prepared according to *Org. Synth.* 1984, 62, 187.

7. After approximately two-thirds of the Grignard reagent is added, a large amount of white precipitate appears.

8. The mixture becomes yellow which is the color of trimethylsilyldiazomethane.

9. The color of the distillate is pale yellow because of co-distillation of trimethylsilyldiazomethane. Therefore, the rate of concentration is very important. If the rate of concentration is more rapid, the yield of trimethylsilyldiazomethane will decrease.

10. The submitters report that when a 30-cm Widmer column is used, the concentration time required is shorter (about 4 hr).

11. Hexane was purified by distillation.

12. The infrared spectrum (hexane) has absorptions at 2075, 1260, and 855 cm^{-1} . The ^1H NMR spectrum is as follows (hexane) δ : 0.16 (s, 9 H), 2.58 (s, 1 H) (internal chloroform standard).

13. The ^1H NMR of the hexane solution showed the presence of a trace of diethyl ether. The concentration of trimethylsilyldiazomethane was determined by the ^1H NMR analysis as follows: Ninety-one milligrams of dibenzyl was dissolved in 1 mL of a hexane solution of trimethylsilyldiazomethane, and its ^1H NMR spectrum was determined. The concentration (\times mmol/mL) of trimethylsilyldiazomethane was calculated as follows:

$$x = 2b/a \text{ (mmol/mL)}$$

a = Integral value (mm) of the methylene protons
(δ : 2.99) of dibenzyl.

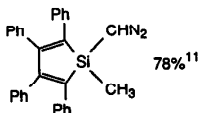
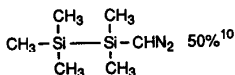
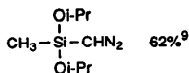
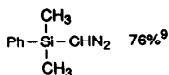
b = Integral value (mm) of the methine proton
(δ : 2.58) of trimethylsilyldiazomethane.

3. Discussion

Trimethylsilyldiazomethane, as a stable and safe substitute for hazardous diazomethane, is useful both as a reagent for introducing a C_1 -unit and as a C-N-N synthon for the preparation of azoles.⁴ Many methods are described in the literature for the preparation of trimethylsilyldiazomethane, including the trimethylsilylation of diazomethane (7-74%),⁵ the alkaline decomposition of N-nitroso-N-(trimethylsilylmethyl)amides (25-61%)^{2,6} and the diazo group transfer reaction of trimethylsilylmethyl lithium with p-toluenesulfonyl azide (38%).⁷ The present modified diazo group transfer method appears to be the most practical, high-yield, and large scale procedure for the preparation of trimethylsilyldiazomethane.⁸

Diphenyl phosphorazidate can be replaced with diethyl phosphorazidate in the above procedure. Use of other azides such as p-toluenesulfonyl azide, p-methoxybenzylloxycarbonyl azide, diphenylphosphinic azide, or diphenylthiophosphinic azide is less satisfactory. No reaction occurs when trimethylsilyl azide, dimethylthiophosphinic azide, or alkaline azides are used, while decomposition of formed trimethylsilyldiazomethane seems to occur when methanesulfonyl azide is used.⁹

The present procedure affords a general method for preparing silyldiazomethanes from the corresponding chloromethylsilyl compounds. Typical examples are as follows:



1. Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan.
2. Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 3249.
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11. Ando, W.; Tanikawa, H.; Sekiguchi, A. *Tetrahedron Lett.* **1983**, *24*, 4245.

Appendix

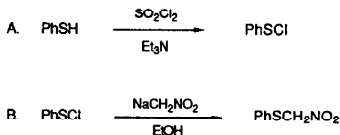
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Chloromethyltrimethylsilane: Silane, (chloromethyl)trimethyl-
(8, 9); (2344-80-1)

Diphenyl phosphorazidate: Phosphorazidic acid, diphenyl ester
(8, 9); (26386-88-9)

Trimethylsilyldiazomethane: Silane, (diazomethyl)trimethyl-
(8, 9); (18107-18-1)

(PHENYLTHIO)NITROMETHANE
(Benzene, [(nitromethyl)thio]-)



Submitted by Anthony G. M. Barrett, Dashyant Dhanak, Gregory G. Graboski, and Sven J. Taylor.¹

Checked by Zhou Zu-liang and Ekkehard Winterfeldt.

1. Procedure

CAUTION: Thiophenol (stench!!) and sulfuryl chloride are highly toxic. Steps A and B should be carried out in an efficient fume hood while wearing gloves and adequate eye protection. Sodium nitromethylate is explosive when dry and should be handled only as a slurry.

A. Phenylsulfenyl chloride. A 250-mL, three-necked, round-bottomed flask, fitted with a nitrogen inlet, pressure-equalizing 125-mL dropping funnel, and magnetic stirring bar, is charged with thiophenol (21 mL) (Note 1), dry triethylamine (0.25 mL) and dry pentane (100 mL) (Note 2) under a blanket of nitrogen. The remaining neck of the flask is stoppered and the nitrogen is allowed to sweep gently through the flask and out of the pressure-equalizing dropping funnel. The flask and its contents are cooled to 0°C with an ice bath and stirring is begun. The dropping funnel is charged with sulfuryl chloride (19 mL) (Note 1). The sulfuryl chloride is added dropwise

over a period of 1 hr to the chilled thiophenol solution with stirring. During this addition, a thick layer of white solid forms. It gradually dissolves as it is broken down. After the addition is complete, the ice bath is removed and the mixture is allowed to stir for 1 hr longer while slowly warming to room temperature. During the course of the addition and subsequent stirring, the clear, pale yellow solution becomes dark orange-red. The dropping funnel is replaced with an outlet adapter connected to a vacuum pump and the nitrogen inlet is exchanged for a ground glass stopper. The pentane and excess sulfonyl chloride are removed under reduced pressure at room temperature. The outlet adapter is replaced by a short-path distillation apparatus adapted for use under reduced pressure. The oily red residue is distilled to give phenylsulfonyl chloride as a blood-red liquid (26 g, 87%), bp 41-42°C (1.5 mm) (Note 3). This compound is stored under nitrogen until used in part B (Note 4).

B. (*Phenylthio*)nitromethane. Freshly cut sodium metal (4.8 g) is added to absolute ethanol (100 mL) in a 500-mL Erlenmeyer flask with a ground glass joint and allowed to react until the metal is completely consumed (Note 5). To this mixture is added a solution of nitromethane (12 g) (Note 6) in absolute ethanol (100 mL) with swirling. The phenylsulfonyl chloride (prepared earlier) is quickly poured into a 1000-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer, nitrogen inlet/outlet adapter and a calcium chloride drying tube, and diluted with dry tetrahydrofuran (THF) (250 mL) (Note 7). Stirring is begun, the drying tube is removed, and the sodium nitromethane-ethanol slurry is added quickly in one portion to the THF solution (Note 8). The deep red solution immediately turns yellow and stirring is continued for a further 10 min. The reaction mixture consists of solid and liquid. It is dissolved in 200 mL of a 1 N sodium hydroxide

solution and poured into a 1000-mL separatory funnel. Dichloromethane (200 mL) is added (Note 9), the aqueous layer (lower layer) is separated and the organic layer further extracted with 1 N sodium hydroxide (2 x 100 mL) (Note 10). The combined aqueous layers are washed with dichloromethane (500 mL) and acidified to pH 3 using 1 N hydrochloric acid. The brown organic layer that appears is separated, diluted with 50 mL of dichloromethane, dried over magnesium sulfate, filtered and concentrated at water aspirator pressure to give 18-19 g (60-65%) of crude (phenylthio)nitromethane as an orange-red oil. This material is of sufficient purity for many purposes. Further purification may be effected by distilling at reduced pressure to give (phenylthio)nitromethane (14 g, 50%) as a pale yellow oil, bp 85-95°C/0.05 mm (Notes 11-14).

2. Notes

1. Thiophenol (97%) and sulfuryl chloride (97%) were obtained from the Aldrich Chemical Company, Inc. and used without further purification.

2. Both pentane and triethylamine were obtained from the Aldrich Chemical Company, Inc. Before use they were dried over sodium wire and distilled from fresh sodium wire onto 4 Å molecular sieves under an atmosphere of nitrogen.

3. The submitters report isolated yields of phenylsulfenyl chloride of 82-92%.

4. Phenylsulfenyl chloride decomposes rapidly in moist air, and should be handled and stored under dry nitrogen.

5. The reaction is exothermic; cooling in an ice bath may be necessary to prevent the ethanol from refluxing.

6. Nitromethane was obtained from the Eastman Kodak Chemical Company and used without further purification.

7. Tetrahydrofuran was obtained from the Baker Chemical Company and distilled from sodium benzophenone ketyl before use.

8. The submitters preferred to transfer the phenylsulfonyl chloride via cannula. The sodium nitromethane-ethanol slurry is added by attaching the Erlenmeyer flask containing it to the reaction flask via an angle adapter and then simply inverting the Erlenmeyer flask. In either method additional absolute ethanol may be necessary to complete the latter addition.

9. Dichloromethane was purchased from the Baker Chemical Company and used without further purification.

10. The checkers used sodium hydroxide (3 x 100 mL) in one run which improved the yield about 5%.

11. During the distillation gases are evolved.

12. A pump of sufficient capacity must be used to maintain reduced pressure of at least 0.10 mm or extensive decomposition results.

13. (Phenylthio)nitromethane has the following properties: ^1H NMR (CDCl_3 , 90 MHz) δ : 5.45 (s, 2 H, CH_2), 7.25-7.5 (m, 5 H, aromatic); IR (film) cm^{-1} : 3060 m, 3025 m, 2960 m, 2905 m, 1960 w, 1885 w, 1810 w, 1550 s, (NO_2), 1485 s, 1475 s, 1440 s, 1390 s, 1355 s, (NO_2), 1260 s, 1185 s, 1070 m, 1025 m, 1005 w, 900 m, 805 m, 745 s, 690 s.

14. *Storage and handling of (phenylthio)nitromethane.* Although (phenylthio)nitromethane will slowly decompose at room temperature, the submitters have found that the compound may be stored essentially unchanged in a freezer at -25°C . Since it has an unpleasant odor, it is best handled in a well ventilated hood; any spillage may be cleaned up with commercial bleach.

3. Discussion

(Phenylthio)nitromethane is a convenient reagent for the synthesis of derivatives of 3-methylfuran,² for the preparation of α -substituted phenylthio esters via the homologation of aldehydes,³ and for the preparation of bicyclic β -lactams from monocyclic precursors.⁴ This method is an adaption of Seebach's procedure.⁵ Alternatively, (phenylthio)nitromethane may be prepared from the nitration of the dianion derived from (phenylthio)acetic acid² or from ethyl nitroacetate and N-(phenylthio)morpholine.⁶ Neither of these procedures are as convenient on a large scale.

1. Department of Chemistry, Northwestern University, Evanston, IL 60201.
2. Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.
3. Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1986**, *51*, 1012.
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5. Seebach, D.; Lehr, F. *Helv. Chim. Acta* **1979**, *62*, 2239.
6. Bordwell, F. G.; Bartmess, J. E. *J. Org. Chem.* **1978**, *43*, 3101.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(Phenylthio)nitromethane: Benzene, [(nitromethyl)thio]- (9); (60595-16-6)

Thiophenol: Benzenethiol (8,9); (108-98-5)

Sulfuryl chloride (8,9); (7791-25-5)

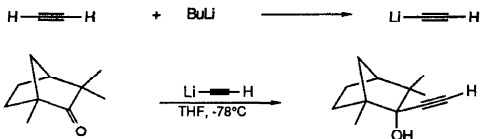
Sodium nitromethylate: Methane, nitro-, ion(1-), sodium (8,9); (25854-38-0)

Phenylsulfenyl choride: Benzenesulfenyl chloride (8,9); (931-59-9)

Nitromethane: Methane, nitro- (8,9); (75-52-5)

PREPARATION AND USE OF LITHIUM ACETYLIDE:

1-METHYL-2-ETHYNYL-endo-3,3-DIMETHYL-2-NORBORNANOL



Submitted by M. Mark Midland, Jim I. McLoughlin, and Ralph T. Werley, Jr.¹

Checked by Matthew J. Sharp and Larry E. Overman.

1. Procedure

An oven-dried (Note 1), 500-mL, septum-capped, round-bottomed flask is flushed with nitrogen, charged with 70 mL of tetrahydrofuran (THF) (Note 2) and cooled to -78°C . After the apparatus has cooled, 157 mL of a 2.1 M solution of butyllithium (0.330 mol) (Note 3) is added using a 50-mL syringe. The contents are mixed by swirling the flask and kept at -78°C until needed. An oven-dried, 2-L, round-bottomed flask, equipped with a magnetic stir bar and capped with a septum, is cooled under a nitrogen purge (Note 4). The flask is charged with 500 mL of THF and cooled to -78°C . A 100-mL graduated cylinder (Note 5) is fitted with a septum in which an 8-mm hole has been bored (Note 6). A 9-mm glass tube which can be connected to either a nitrogen or acetylene line through a three-way valve (Notes 6 and 7) is inserted through the septum of the graduated cylinder. A double-ended needle is used to connect the cylinder to the 2-L reaction flask. After the cylinder

and reaction flask have been thoroughly purged with nitrogen, 70 mL of THF is introduced into the cylinder, and the cylinder is cooled to -78°C (Note 8). Acetylene (Notes 7 and 9) is introduced through the 9-mm tube into the bottom of the graduated cylinder at such a rate that 30 mL (Note 10) has been added in 20 min; excess acetylene which does not dissolve in the THF is allowed to flow through the double-ended needle to the 2-L reaction flask. The cold acetylene solution is transferred via the double-ended needle to the 2-L reaction flask. While the solution is cooling in the -78°C bath, nitrogen is blown over the surface to purge completely the system of acetylene (Note 11). The precooled butyllithium/THF solution is then slowly added by a double-ended needle over a period of 1 hr (Note 12). The clear solution of lithium acetylide is stirred for an additional 15 min at -78°C before 48.4 mL of (-)-fenchone (0.300 mol, Note 13) is slowly added via syringe. The solution immediately becomes yellow. After the addition is complete, the cold bath is removed and the mixture is stirred for 3 hr while it warms to room temperature. The flask is opened to the atmosphere and 400 mL of 1.0 M hydrochloric acid is added (Note 14). The quenched reaction is stirred for 20 min and then transferred to a 2-L separatory funnel. The aqueous material is separated and 200 mL of pentane is added. The organic layer is then sequentially washed with 100 mL of 1.0 M hydrochloric acid, 300 mL of water and finally 100 mL of saturated brine. The combined aqueous material is extracted with 200 mL of ether. The organic extracts are combined, dried with magnesium sulfate and filtered. Concentration (rotary evaporation, 40°C under aspirator pressure) provides a thick yellow oil which is distilled to obtain 48.2 g (90%) of the alcohol as a pale yellow oil (bp $51-55^{\circ}\text{C}/0.05$ mm) (Note 15).

2. Notes

1. All glassware was oven-dried for at least 24 hr at 130°C, assembled hot and cooled under a stream of nitrogen.²

2. Tetrahydrofuran, THF, was obtained from Mallinckrodt Inc. and distilled from sodium/benzophenone ketyl immediately prior to use.

3. The checkers used butyllithium purchased from Lithium Alkyls which was standardized by titration with 2,5-dimethoxybenzyl alcohol. The submitters used butyllithium obtained from Aldrich Chemical Company, Inc. as a 1.55 M solution in hexanes which was measured by transfer to a septum-capped 250-mL graduated cylinder with a 15-gauge cannula and nitrogen back pressure.^{2a} This solution was then transferred to the flask containing THF in the same manner. The THF must be cooled prior to addition of the butyllithium. Stainless steel double-ended needles of the type used by the submitters are available from Aldrich Chemical Company, Inc. and Ace Glass, Inc.

4. A slight positive pressure of nitrogen was maintained in the reaction vessel throughout the procedure until the reaction was quenched.

5. Graduated cylinders of various sizes with 24/40 standard taper joints are available from Ace Glass, Inc.; appropriate septa were obtained from Aldrich Chemical Company, Inc.

6. Both nitrogen and acetylene are introduced into the graduated cylinder through a 9-mm glass tube approximately 30 cm in length. An 8-mm hole bored through the septum allows for a good seal and for movement of the glass tube in order to adjust the height of the tube from the bottom of the graduated cylinder. A drawing of the apparatus employed is provided in Figure 1.

7. Acetylene is obtained from Liquid Carbonics and is purified by passage through a -78°C cold trap, a liquid trap (to prevent aspiration of sulfuric acid), a gas washing bottle containing 100 mL of concd sulfuric acid and a calcium chloride drying tube before introduction into the graduated cylinder.³ A bubbler and a 3-way valve, in that order, are placed before the graduated cylinder. The bubbler with a head of 30 mm of mercury is connected to the system with a T-shaped connecting tube and serves as a relief valve to prevent over pressurization of the acetylene line. The 3-way valve allows nitrogen to be flushed through the graduated cylinder and reaction flask for purging the apparatus and to provide back pressure for the transfer of the acetylene solution. See Figure 1 for a drawing of the reaction apparatus.

Caution: Reactions with acetylene should be carried out in the hood and all lines carrying exhaust from the bubblers must be vented to a fume hood!

8. The graduated cylinder and its contents are cooled in a wide-mouth Dewar containing a dry ice/acetone slurry.

9. Acetylene is an explosive compound and reacts with metals (e.g., Cu, Ag).⁴

10. The amount of acetylene is approximated by assuming a density of 0.7 g/mL. Approximately 2.5-3.0 equiv of acetylene is used. THF is added to the graduated cylinder so that the final volume of the acetylene solution will be 100 mL. In this case, 30 mL of acetylene is measured to provide approximately 0.85 mol.

11. Acetylene gas must be removed from above the solution to prevent reaction with the concentrated butyllithium solution entering the flask. Such a reaction in the presence of excess butyllithium will result in the formation of dilithium acetylide on the needle tip. The formation of even small amounts of dilithium acetylide must be avoided; lithium acetylide readily

disproportionates to dilithium acetylide and acetylene upon warming or in the presence of excess butyllithium. The formation of a small amount of dilithium acetylide accelerates the rate of disproportionation (see: Note 12).⁵

12. Butyllithium must be added slowly to an excess of the efficiently stirred acetylene solution at -78°C . Localized warming of the solution or rapid introduction of butyllithium to produce a local excess of base must be avoided in order to prevent the formation of the unreactive and insoluble dilithium acetylide which will be observed as a cloudy suspension. Reaction of ketones or aldehydes with a cloudy suspension of dilithium acetylide results in substantially lowered yields of the carbinol products.⁵

13. (-)-Fenchone was obtained from Fluka Chemical Corporation and was used without additional purification.

14. After the solution is warmed to room temperature, substantial amounts of acetylene and butane may remain in solution. The reaction must be quenched in an efficient fume hood, and the first 10-20 mL of hydrochloric acid solution should be added slowly.

15. The product displays the following physical and spectral data: $[\alpha]_D^{25} +20.4^{\circ}$ (CHCl_3 , c 9); IR (neat film/NaCl plates) cm^{-1} : 3490, 2110, 1460, 1060; ^1H NMR (200 MHz, CDCl_3) δ : 0.93 (s, 3 H), 1.0-1.15 (m, 2 H), 1.11 (s, 3 H), 1.17 (s, 3 H), 1.20-1.95 (m, 5 H), 1.99 (OH), 2.53 (s, 1 H); ^{13}C NMR (50 MHz, CDCl_3) δ : 17.84, 21.54, 25.77, 27.08, 29.81, 40.95, 42.90, 48.40, 53.06, 74.86, 80.45, 85.61; MS (EI, -70 eV): m/z calcd. for $\text{C}_{12}\text{H}_{18}\text{O}$: 178.1357, m/z found: 178.1355. The product is a 97:3 mixture of endo:exo addition products based upon capillary GC analysis. (A Hewlett Packard 5880 Capillary Gas Chromatograph equipped with Supelcowax-10 30-m capillary column available from Supelco, Inc. was used.)

3. Discussion

A general procedure for the preparation and use of monolithium acetylide is described. Monolithium acetylide is a useful reagent for the preparation of a variety of propargyl alcohols and terminal acetylenes.⁶ The formation of monolithium acetylide is often complicated by the production of dilithium acetylide.⁷ The reagent may be formed in liquid ammonia which serves to stabilize the monoanion. Other amines, such as ethylenediamine, may be similarly added as a complexing agent.⁸ However, it is often desirable to prepare the more reactive amine-free acetylide species.^{5,7b} Dilithium acetylide is an insoluble salt in tetrahydrofuran and is generally unreactive toward ketones, aldehydes, and other electrophiles. The slow addition of a dilute, cooled solution of butyllithium is critical for the reproducible preparation of a clear lithium acetylide solution. Solutions of monolithium acetylide must be kept cold, near -78°C , to prevent disproportionation to dilithium acetylide and acetylene. If the solution is warmed to 0°C , irreversible formation of dilithium acetylide as the white insoluble precipitate occurs.

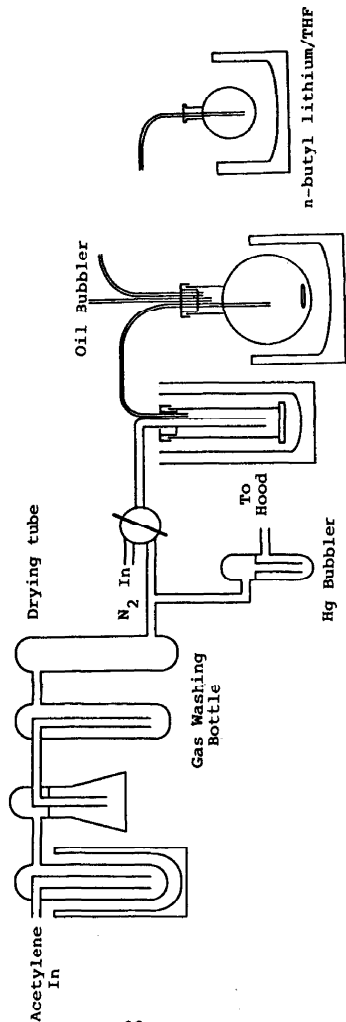
Lithium acetylide adds in high yield to a variety of ketones and aldehydes (Table I). Typically, 1.1 to 1.2 equiv of lithium acetylide is employed. Sterically-hindered ketones react in higher yield when 2.0 equiv of lithium acetylide is used. Optimum yields are obtained with a concentration of monolithium acetylide of approximately 0.5 M; higher concentrations, approaching 1.0 M, usually result in slightly lowered yields.⁵ In all cases the reactions are essentially complete upon warming to room temperature. This method allows for a rapid and convenient preparation of propargyl alcohols. The procedure seems to be generally applicable to a wide variety of ketones and aldehydes.

TABLE I
ADDITION OF MONOLITHIUM ACETYLIDE TO ALDEHYDES AND KETONES

Ketone RCOR'		
R	R'	Yield (%) ^a
CH_3	CH_3	94
$\text{CH}_3(\text{CH}_2)_4$	H	98
CH_3	$(\text{CH}_2)_3\text{CH}_3$	92
$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2$	$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2$	75, 86 ^b
$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)$	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)$	89
$(\text{CH}_3)_3\text{C}$	$(\text{CH}_3)_3\text{C}$	66, 98 ^b
PhCH_2	CH_3	94
Ph	CH_3	75
Ph	H	93
Ph	Ph	(85)
$\text{PhCH}=\text{CH}$	H	96
$(\text{CH}_3)_2\text{C}=\text{CH}$	CH_3	86(77)
β -Inone		93
cyclo- $(\text{CH}_2)_4$		94
cyclo- $(\text{CH}_2)_5$		95
cyclo- $(\text{CH}_2)_6$		90(83)
cyclo- $(\text{CH}_2)_7$		86
Norcamphor		97(92) ^c
Cyclohexanecarboxaldehyde		98

^aBy VPC based on RCOR'. Isolated yields are in parentheses. ^b100% Excess monolithium acetylide was used. ^cThe product was >99% 2-ethynyl-endo-2-norbornanol by VPC and ¹³C NMR examination.

Figure 1



1. Department of Chemistry, University of California, Riverside, CA 92521.
2. (a) Techniques for handling air sensitive compounds are discussed in: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Synthesis via Boranes"; Wiley: New York, 1975; (b) Technical data for handling air sensitive compounds may also be obtained from Aldrich Chemical Company, Inc.: Lane, C. F.; Kramer, G. W. *Aldrichimica Acta* **1977**, *10*, 11-16.
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4. Vogel, A. I.; Furniss, B. J.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. "Textbook of Practical Organic Chemistry", 4th ed.; Longman Inc.: New York, 1978; p. 9.
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6. Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis", Wiley: New York, 1967; Vol. 1, pp. 573-574.
7. (a) Corbellini, M.; Turner, L. *Chim. Ind. (Milan)* **1960**, *42*, 251; *Chem. Abstr.* **1960**, *54*, 19250f; (b) Bradsmas, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes and Cumulenes: A Laboratory Manual"; Elsevier: New York, 1981; pp. 9-12.
8. Beumel, O. F., Jr.; Harris, R. J. *J. Org. Chem.* **1963**, *28*, 2775.

Appendix

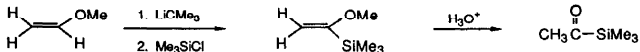
Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

Monolithium acetylide: Lithium acetylide (8,9); (1111-64-4)

(-)-Fenchone: 2-Norbornanone, 1,3,3-trimethyl- (8); Bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl- (9); (1195-79-5)

ACETYLTRIMETHYLSILANE
(Silane, acetyltrimethyl-)



Submitted by John A. Soderquist.¹

Checked by Edward D. White III and James D. White.

1. Procedure

Caution! Persons following these procedures should be thoroughly familiar with the handling of air-sensitive solutions (Note 1).

A dry (Note 2), 2-L, round-bottomed flask containing a magnetic stirring bar and equipped with a rubber septum inlet is flushed with dry nitrogen and charged with 450 mL of purified tetrahydrofuran (Note 3). After the contents of the flask are cooled using a dry ice/acetone bath, 72 g (1.2 mol) of methyl vinyl ether is distilled into the flask from a commercial cylinder (Note 4). The septum is replaced, under a positive pressure of nitrogen gas, with a 500-mL, pressure-equalizing addition funnel equipped with a rubber septum inlet. The stirred contents of the flask are continuously cooled while 1.0 mol of tert-butyllithium in pentane solution (*Caution! Solutions of this reagent are pyrophoric and extreme care should be exercised when carrying out this manipulation!*) (Note 5) is transferred to the addition funnel and subsequently added to the mixture dropwise over ca. 1.5 hr. The resulting yellow slurry is allowed to warm slowly to 0°C over ca. 3 hr (Note 6). With the addition of dry ice to the bath, the near-colorless solution is recooled to ca. -78°C and

84.6 g (0.78 mol) of chlorotrimethylsilane (Note 7) is transferred to the addition funnel and subsequently added dropwise to the stirred mixture. The cold bath is removed and, after the mixture has reached room temperature, it is allowed to stir for an additional 1 hr (Note 8). The contents of the flask are carefully poured into a 2-L separatory funnel which contains ca. 400 g of ice and ca. 200 mL of saturated ammonium chloride solution (Note 9). After separation of the aqueous layer, the organic solution is washed with water (12 x 250 mL) (Note 10), dried over anhydrous potassium carbonate, filtered and distilled to give 89-95 g (88-94%) of 1-(methoxyvinyl)trimethylsilane (bp 102-104°C, 760 mm), n_D^{20} 1.4173 (Notes 11 and 12).

A 500-mL, round-bottomed flask is charged with 65 g (0.50 mol) of 1-(methoxyvinyl)trimethylsilane and 300 mL of a 4:1 v/v mixture of acetone and 1.0 M aqueous hydrochloric acid (Note 13). After the pale yellow-green solution is stirred for 1 hr at room temperature, it is transferred to a 1-L separatory funnel and 150 mL each of water and diethyl ether are added. After separation, the aqueous layer is washed with diethyl ether (2 x 50 mL), and these extracts are combined with the organic material. The ethereal solution is washed with water (3 x 300 mL), dried over anhydrous magnesium sulfate, filtered and distilled to give 45-48 g (78-83%) of acetyltrimethylsilane (bp 112°C, 760 mm), n_D^{20} 1.4125 [lit.² 1.4113] (Notes 14 and 15).

2. Notes

1. For a detailed description of the general techniques used in the handling of air-sensitive solutions, consult ref. 3. Alternatively, a useful pamphlet describing these techniques is available from Aldrich Chemical Company, Inc., upon request.

2. All of the glassware used in the preparation of 1-(methoxyvinyl)-trimethylsilane was dried for at least 4 hr at 110°C, assembled hot and allowed to cool under a nitrogen atmosphere.

3. Reagent-grade tetrahydrofuran (Aldrich Chemical Company, Inc.) was distilled under a nitrogen atmosphere from sodium/benzophenone prior to use.

4. Commercial cylinders of methyl vinyl ether were obtained from Matheson Gas Products, East Rutherford, NJ, and were fitted with a standard needle-valve regulator adapted to connect to a 24 in. 16-gauge syringe needle (Aldrich Chemical Company, Inc.). Unwanted, non-volatile impurities from the cylinder were removed by employing a second flask, which was empty and septum-sealed, between the cylinder and the cold reaction flask. The gaseous reagent is transferred, through the needle, into the empty flask and through a double-ended needle (Aldrich Chemical Company, Inc.) into the reaction flask. The weight of the added methyl vinyl ether was periodically determined from the difference between the initial tare weight of the flask plus the contents and the total weight at each new weighing. However, the amount of this reagent added can be varied by at least +/- 10% without significantly affecting the product yield.

5. This reagent was obtained either from Aldrich Chemical Company, Inc., or Lithium Corporation of America, Bessemer City, NC. A technical data sheet is available from the suppliers. Solutions of ca. 2 M were titrimetrically analyzed for active alkylolithium by the tosylhydrazone method.⁴ It is advisable to make certain that the organolithium reagent to be used was prepared in pentane solution. This evaluation can be easily accomplished by the gas chromatographic analysis of the organic layer obtained from the hydrolysis, under a nitrogen atmosphere, of the tert-butyllithium solution to be used. Isobutane and pentane should comprise essentially all of the

volatile material observed. Recently, from the latter supplier, we found that the solvent used was a petroleum distillate which contained some higher boiling components. As a consequence, the distillative isolation of the product was more difficult and the yield was lower (i.e., 80%).

6. The slow warm-up is accomplished conveniently by the removal of the solid dry ice from the cold bath. This process minimizes the formation of acetylenic by-products. The warm-up period can vary with the amount of coolant used. We have consistently obtained good results using sufficient coolant to match the liquid level of the reaction mixture.

7. Chlorotrimethylsilane was purchased from Petrarch, Inc., Levittown, PA and was distilled from calcium hydride prior to use.

8. Lithium chloride precipitates during the warm-up procedure.

9. *CAUTION! The reaction mixture contains low boiling components and care must be exercised to prevent product loss.*

10. This procedure effectively removes the tetrahydrofuran, thus simplifying the distillative isolation of the product. This operation must be done carefully to prevent the loss of product.

11. A Nester-Faust Model NFT-50 annular spinning-band distillation unit was used to obtain the reported product yields in >99% chemical purity by gas chromatographic analysis (Perkin-Elmer Model Sigma 1B Instrument using a 6' x 1/8" 5% SE-30 on silylated Chromosorb W column). Lower product yields (84-86%) of similar chemical purity were obtained using a 200-mm column packed with glass helices.

12. This product gave a satisfactory combustion analysis for $C_6H_{14}OSi$ and exhibited the following spectroscopic data: 1H NMR ($CDCl_3$) δ : 0.09 (s, 9 H), 3.50 (s, 3 H), 4.28 (d, 1 H, $J = 2.0$), 4.59 (d, 1 H, $J = 2.0$); ^{13}C NMR ($CDCl_3$) δ : -2.3 (Si- CH_3), 54.0 (O CH_3), 93.3 (C-2), 170.1 (C-1); IR (film)

cm^{-1} : 1590 (C=C); 1257 (TMS); 1227, 1050 (C=C-OR); MS: m/z 130 (6%); 115 (20%); 89 (47%); 73 (100%); 59 (29%); 44 (11%); 42 (15%).

13. Exposure to direct sunlight was routinely avoided because of the known photochemical reactivity of acylsilanes.⁵

14. Distillation and gas chromatographic analysis of this compound was carried out as described in Note 11.

15. This product gave a satisfactory combustion analysis for $\text{C}_5\text{H}_{12}\text{OSi}$ and exhibited the following spectroscopic data: ^1H NMR (CDCl_3) δ : 0.09 (s, 9 H), 2.16 (s, 3 H); ^{13}C NMR (CDCl_3) δ : -3.5 (Si-CH₃), 35.2 (CH₃), 246.8 (C=O); IR (film) cm^{-1} : 1645 (C=O); MS: m/z 116 (13%), 101 (11%), 73 (100%), 59 (6%), 44 (34%), 42 (15%). The ultraviolet spectrum of this material in cyclohexane solution exhibits absorbances at 381, 365, 356, and 344 nm with molar extinction coefficients of 91, 123, 97, and 60, respectively. In addition, shorter wave-length shoulders are observed. For a detailed discussion of the spectroscopic properties of acylsilanes, consult ref. 6.

3. Discussion

Acylsilanes have been known since 1957 when Brook described the synthesis of benzoyltriphenylsilane.⁷ Their unique reactivity has made them very useful reagents for organic syntheses.⁸ The simplest known member of this class of compounds, acetyltrimethylsilane, has been prepared from the oxidation of 1-trimethylsilylethanol,⁶ the hydrolysis of 2-methyl-2-trimethylsilyl-1,3-dithiane,² the silylation/hydrolysis of *N*-acetylimidazole,⁹ the lithiation/silylation/hydrolysis of ethyl vinyl ether,¹⁰ and the pyrolysis of 2,4,4-trimethyl-2-trimethylsilyl-1,3-oxathiolane 3,3-dioxide,¹¹ and the silylation of acid chlorides.¹²

The present preparation¹³ utilizes the simple deprotonation of methyl vinyl ether first reported by Baldwin and co-workers to obtain 1-(methoxyvinyl)lithium,¹⁴ which functions as a very useful reagent for nucleophilic acylation.¹⁵ After detailed studies of the processes involved, this approach has been applied to the syntheses of a number of acyl derivatives of silicon, germanium, and tin.¹⁶ This procedure also overcomes the hydrolysis problems encountered in a previous study.¹⁰ The vinyl ether approach to such acylmetalloids has been demonstrated to provide access to systems which cannot be prepared using other acyl anion equivalents.¹⁷ In the present case, the simple two-step process from commercially-available reagents gives the highest reported overall yield of pure acetyltrimethylsilane from chlorotrimethylsilane (69-78%). Moreover, the reaction sequence can be scaled up or down without encountering difficulties.

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ref. 16.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

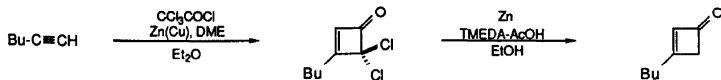
Acetyltrimethylsilane: Silane, acetyltrimethyl- (8,9); (13411-48-8)

Methyl vinyl ether: Ether, methyl vinyl (8); Ethene, methoxy- (9); (107-25-5)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

1-(Methoxyvinyl)trimethylsilane: Silane, (1-methoxyethenyl)trimethyl- (10);
(79678-01-6)

3-BUTYLCYCLOBUTENONE
(2-Cyclobuten-1-one, 3-butyl-)



Submitted by Rick L. Danheiser,^{1a} Selvaraj Savariar, and Don D. Cha.^{1b}

Checked by Reinhard Kratzberg and Ekkehard Winterfeldt.

1. Procedure

3-Butyl-4,4-dichlorocyclobutenone. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers, and a 250-mL pressure-equalizing addition funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 39.23 g (0.60 mol) of zinc-copper couple (Note 2), 400 mL of diethyl ether (Note 3), and 23.0 mL (0.20 mol) of 1-hexyne (Note 4). The dropping funnel is charged with a solution of 44.6 mL (0.40 mol) of trichloroacetyl chloride (Note 5) in 125 mL of dimethoxyethane (Note 6), and this solution is then added dropwise to the reaction mixture over 1 hr. After 18 hr, the resulting brown mixture is filtered through a sintered-glass Büchner funnel, and the black solid which is separated is thoroughly washed with 200 mL of hexane. The filtrate is washed successively with 200 mL each of ice-cold 0.5 N hydrochloric acid, ice-cold 5% sodium hydroxide solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated at reduced pressure using a rotary evaporator. The residual brown oil is transferred to a 100-mL, round-bottomed

flask and distilled through a 10-cm Vigreux column to afford 29.5-30.0 g (76-78%) of 3-butyl-4,4-dichlorocyclobutenone as a colorless liquid, bp 68.5-70°C (0.3 mm) (Note 7).

3-Butylcyclobutenone. A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two glass stoppers, and a 125-mL pressure-equalizing dropping funnel fitted with a nitrogen inlet adapter (Note 1). The flask is charged with 52.6 g (0.805 mol) of zinc dust (Note 8), 121 mL of tetramethylethylenediamine (Note 9), and 270 mL of absolute ethanol, and cooled with an ice bath while 46 mL of glacial acetic acid is added dropwise over 5 min. The reaction mixture is maintained at 0°C while a solution of 26.59 g (0.138 mol) of 3-butyl-4,4-dichlorocyclobutenone in 27 mL of absolute ethanol is added over 10 min via the dropping funnel. After 15 min the ice bath is removed, and the reaction mixture is stirred for 2.5 hr and then filtered through a sintered glass Büchner funnel with the aid of 1.5 L of a 1:1 mixture of diethyl ether and pentane. The filtrate is washed successively with 500 mL of 1 N hydrochloric acid, 500 mL of water, 800 mL of saturated sodium bicarbonate solution, and 500 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The residual yellow oil is transferred to a 100-mL, round-bottomed flask fitted with a short-path distillation head (Note 10) and a pear-shaped receiver flask which is cooled below -75°C with a dry ice-acetone bath. Distillation at 0.001 mm (bath temperature 50-70°C) (Note 11) provides 3-butylcyclobutenone (13.4-16.2 g, 78-86% yield) as a clear, colorless liquid, bp 33°C (0.001 mm) (Note 12).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven and then assembled and maintained under an atmosphere of nitrogen during the course of the reaction.

2. To a stirred mixture of 65.38 g (1.0 mol) of zinc dust (purchased from Mallinckrodt Inc.) and 100 mL of water in a 1-L Erlenmeyer flask is added at 30-sec intervals two solutions of 7.6 g of copper sulfate, ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) in 50 mL of water. After 1 min the mixture is filtered through a sintered-glass Büchner funnel and the zinc-copper couple is washed with two 50-mL portions of water, two 50-mL portions of acetone, and 50 mL of diethyl ether. The resulting dark gray powder is dried at 100°C at 1 mm for 4 hr and then stored under nitrogen.

3. Diethyl ether was distilled from sodium benzophenone ketyl immediately before use.

4. 1-Hexyne was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride before use.

5. Trichloroacetyl chloride was purchased from Fluka Chemical Corporation and distilled before use.

6. Dimethoxyethane was obtained from Aldrich Chemical Company, Inc., and distilled from sodium benzophenone ketyl immediately before use.

7. The product exhibits the following spectral properties: IR (film) cm^{-1} : 2970, 2940, 2880, 1800, 1585, 1475, 1415, 1390, 1260, 1210, 1045, 850, and 630; UV (isooctane) nm max (ϵ): 306 (33) and 215 (9530); ^1H NMR (300 MHz, CDCl_3) δ : 0.96 (t, 3 H, $J = 7$), 1.45 (apparent sextet, 2 H, $J = 7$), 1.72 (apparent quintet, 2 H, $J = 7$), 2.69 (dt, 2 H, $J = 2, 7$), and 6.20 (t, 1 H, $J = 2$); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 13.5, 22.3, 25.9, 27.6, 91.9, 135.6, 179.2, and 186.1.

8. Zinc dust was purchased from Mallinckrodt Inc. and used without further purification.

9. Tetramethylethylenediamine (TMEDA) was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride before use.

10. The delivery tube of the short-path distillation head is fitted with a 5-cm length of Teflon tubing which extends nearly to the bottom of the receiving flask.

11. Substantial decomposition of the product was observed if the bath temperature was allowed to exceed 80°C or if distillation was attempted using a short Vigreux column.

12. 3-Butylcyclobutenone displays the following spectral properties: IR (film) cm^{-1} : 2970, 2940, 2860, 1770, 1590, 1470, 1420, 1385, 1310, 1280, 1220, 1180, 1100, 1030, 990, 925, and 850; UV (isooctane) nm max (ϵ): 306 (36) and 220 (6860); ^1H NMR (300 MHz, CDCl_3) δ : 0.93 (t, 3 H, $J = 7$), 1.38 (apparent sextet, 2 H, $J = 7$), 1.58 (apparent quintet, 2 H, $J = 7$), 2.54 (t, 2 H, $J = 7$), 3.12 (s, 2 H), and 5.86 (s, 1 H); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 13.5, 22.2, 27.9, 31.6, 50.5, 133.8, 181.2, and 187.6.

3. Discussion

The procedure described above illustrates a general two-step method for the preparation of 3-substituted and 2,3-disubstituted cyclobutenones.^{2,3} The first step in the procedure involves the [2+2] cycloaddition of an acetylene with dichloroketene, which is best carried out using a modification of the method originally reported by Hassner and Dillon.⁴ Under these conditions dichloroketene combines smoothly with a variety of alkyne derivatives in contrast to ketene itself which fails to add to unactivated acetylenes. The

4,4-dichlorocyclobutenone cycloadducts produced in the first step are then subjected to reductive dechlorination with zinc dust to afford the desired cyclobutenones. Although it has previously been reported that this reductive dechlorination reaction cannot be accomplished reliably,⁴ recent studies^{2,3} have shown that under carefully controlled conditions the desired transformation is in fact a feasible and efficient process. As summarized in Table I, this strategy is applicable to the synthesis of a variety of substituted cyclobutenones.

The preparation of 3-butyl-4,4-dichlorocyclobutenone described here represents an optimized procedure for the [2+2] cycloaddition of dichloroketene with acetylenes. Previously there has been some disagreement over the efficacy of phosphorus oxychloride (POCl_3) as a sequestering agent for the zinc chloride generated in the course of the reaction. Hassner and Dillon⁴ have reported that the inclusion of phosphorus oxychloride is crucial to the success of these reactions, and that in its absence tarry products are produced which are difficult to purify. Dreiding and co-workers, however, report that these conditions lead to the production of the desired cycloadducts contaminated with significant amounts of the corresponding 2,4-dichloro isomers. Dreiding consequently suggests that these cycloadditions are best carried out in the absence of phosphorus oxychloride employing short reaction times of less than 15 min.

We have found that the method used to prepare the zinc-copper couple is an important variable in determining the efficiency and rate of these reactions. Optimal results are achieved using a couple prepared by brief (2 min) exposure of commercial zinc dust to twice the amount (0.06 equiv) of copper sulfate employed in the previous studies.^{3,4} We have also found that the cycloadditions proceed with equal efficiency and more conveniently by

employing dimethoxyethane⁵ in place of phosphorus oxychloride as a zinc chloride sequestering agent. Under these optimized conditions a variety of terminal acetylenes are smoothly converted to 4,4-dichlorocyclobutenones in high yield. Although cycloadditions involving disubstituted acetylenes lead to the desired 4,4-dichlorocyclobutenones contaminated with varying amounts of isomeric 2,4-dichloro isomers, the formation of these by-products can be suppressed (to less than 10%) simply by carrying out the cycloaddition at temperatures between 10°C and 15°C.


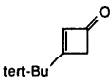
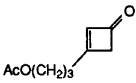

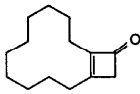

Under conventional dechlorination conditions (20 equiv of zinc dust, acetic acid, 25°C or 50°C) the reduction of 4,4-dichlorocyclobutenones affords complex mixtures of products which include the desired cyclobutenones as well as significant amounts of partially reduced byproducts. We have found that the desired transformation can be accomplished cleanly provided that the reduction is carried out at room temperature in alcoholic solvents (preferably ethanol) in the presence of 5 equiv each of acetic acid and a tertiary amine (preferably tetramethylethylenediamine). Zinc dust has proven to be somewhat superior to zinc-copper couple for this reduction. The desired cyclobutenones are obtained in somewhat higher yield using this procedure as compared to the related conditions reported by Dreiding [Zn(Cu), 4:1 AcOH-pyridine, 50-60°C] for the same transformation.³

The most efficient synthetic route to 3-butylcyclobutenone reported previously⁶ involves the addition of butylmagnesium bromide⁷ or butyllithium⁸ to 3-ethoxycyclobutenone followed by acid hydrolysis. 3-Ethoxycyclobutenone is itself available in modest yield via the addition of ketene to ethoxyacetylene. This procedure provides 3-butylcyclobutenone in only 20% overall yield and requires the use of a ketene generator and the rather unstable ethoxyacetylene as starting material.

Cyclobutenones serve as versatile intermediates for the preparation of α,β -butenolides,⁹ cyclopentenones,⁹ and a variety of substituted cyclobutane derivatives. We have shown that cyclobutenones also function as four-carbon annulation components in routes to eight-membered carbocycles⁸ and highly substituted aromatic compounds.¹⁰

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Table. Synthesis of Cyclobutenones from Alkynes

Case	Alkyne	Cyclobutenone	Isolated Yield (%)
1	$\text{Bu-C}\equiv\text{CH}$		70
2	$\text{tert-Bu-C}\equiv\text{CH}$		54
3	$\text{AcO(CH}_2)_3\text{-C}\equiv\text{CH}$		56
4	$\text{Ph-C}\equiv\text{CH}$		66-77
5	Cyclododecyne		75
6	$\text{Pr-C}\equiv\text{C-Pr}$		73

Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

3-Butylcyclobutenone: 2-Cyclobuten-1-one, 3-butyl- (9); (38425-48-8)

3-Butyl-4,4-dichlorocyclobutenone: 2-Cyclobuten-1-one, 3-butyl-4,4-dichloro-
(10); (72284-70-9)

1-Hexyne (8,9); (693-02-7)

Trichloroacetyl chloride: Acetyl chloride, trichloro- (8,9); (76-02-8)

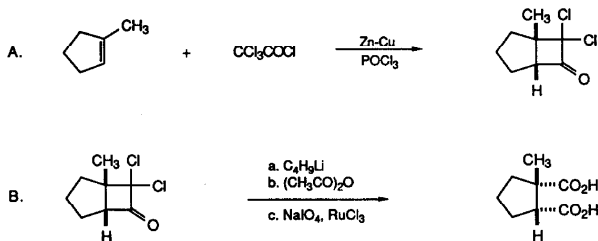
Tetramethylethylenediamine: Ethylenediamine, N,N,N',N'-tetramethyl- (8);

1,2-Ethanediamine, N,N,N',N'-tetramethyl- (9); (110-18-9)

VICINAL DICARBOXYLATION OF AN ALKENE:

cis-1-METHYLCYCLOPENTANE-1,2-DICARBOXYLIC ACID

(1,2-Cyclopentanedicarboxylic acid, 1-methyl-, cis-(±)-)



Submitted by Jean-Pierre Deprés and Andrew E. Greene.¹

Checked by Scott K. Thompson, Gregory A. Slough, and Clayton H. Heathcock.

1. Procedure

A. *7,7-Dichloro-1-methylbicyclo[3.2.0]heptan-6-one*. A 500-mL, two-necked, round-bottomed flask is equipped with a Teflon-covered magnetic stirring bar, a 250-mL pressure-equalizing addition funnel topped with a gas inlet, and a condenser connected to a Nujol-filled bubbler (Note 1). The system is flushed with nitrogen (Note 2). The flask is then charged with 10.0 g (ca. 150 mmol) of zinc-copper couple (Note 3), 200 mL of anhydrous ether (Note 4), and 10.5 mL (8.2 g, 100 mmol) of 1-methyl-1-cyclopentene (Note 5) and the addition funnel is filled with a solution of 13.4 mL (21.8 g, 120 mmol) of trichloroacetyl chloride (Note 5) and 11.2 mL (18.4 g, 120 mmol) of phosphorus oxychloride (Note 6) in 100 mL of anhydrous ether. Magnetic

stirring is begun and the solution is added dropwise over 1 hr to the reaction flask at room temperature. After being stirred for an additional 14 hr, the reaction mixture is filtered under water pump pressure through 30 g of filter aid, which is then washed with 120 mL of ether. The filtrate is concentrated to ca. 100-120 mL, treated with 400 mL of hexane, and then briefly stirred to precipitate the zinc chloride. The supernatant solution is transferred to a separatory funnel and the viscous residue is washed with two 75-mL portions of 3:1 hexane-ether. The combined solution is washed successively with 200 mL of cold water, 200 mL of saturated aqueous sodium bicarbonate solution, and 2 x 50 mL of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated to dryness by rotary evaporation at 25°C to give 17.0-17.8 g of a brown oil. Vacuum distillation of this material without fractionation provides 14.9-16.0 g (77-83%) of 7,7-dichloro-1-methylbicyclo-[3.2.0]heptan-6-one as a clear, light yellow oil, bp 38°C (0.2 mm), n_D^{20} 1.4970 (Note 7).

B. cis-1-Methylcyclopentane-1,2-dicarboxylic acid. A 1-L, one-necked, round-bottomed flask (Note 1) equipped with a Teflon-covered magnetic stirring bar is flushed with nitrogen and then charged with 300 mL of dry tetrahydrofuran (Note 4) and 14.5 g (75 mmol) of 7,7-dichloro-1-methylbicyclo-[3.2.0]heptan-6-one. The flask is capped with a septum and connected to a Nujol bubbler and to a nitrogen line by means of syringe needles (Note 2). To the stirred solution cooled in a dry ice-acetone bath is added by syringe over 5 min 33.2 mL (83 mmol) of a 2.50 M solution of butyllithium in hexane (Note 8). After being stirred for 15 min with continued cooling, the reaction mixture is treated with 14.2 mL (150 mmol) of acetic anhydride all at once (Note 9). The cooling bath is removed and the reaction mixture is allowed to warm to room temperature and then stirred for an additional 1 hr. Most of the

solvent and excess acetic anhydride are directly removed with a rotary evaporator at 25°C under water pump pressure (Note 10). The resulting solid residue is further dried for 15 to 30 min at 4 mm and then dissolved in a mixture of 100 mL of acetonitrile, 100 mL of carbon tetrachloride, and 150 mL of distilled water. The mixture is cooled in an ice bath and, with efficient stirring, treated with 40.1 g (187 mmol) of sodium periodate and 346 mg (1.5 mmol) of ruthenium(III) chloride hydrate (Note 11). After 15 min, the cooling bath is removed (Note 12) and stirring is continued for 5 hr, whereupon the thick mixture is treated with 200 mL of 10% aqueous sodium hydroxide solution and then extracted in a separatory funnel with 500 mL of 1:1 ether-hexane (Note 13). The phases are separated and to the aqueous phase is added 900 mL of 2:1 ether-ethyl acetate followed by a 2 N aqueous hydrochloric acid solution until a pH of 2 to 3 is obtained (Note 14). After being vigorously agitated, the phases are separated and the organic phase is washed successively with solutions of 3% aqueous sodium thiosulfate (Note 15) and saturated aqueous sodium chloride. All aqueous phases are mixed and, at pH 2 to 3, extracted with 1 L of 3:2 ether-ethyl acetate, which is then washed as before. The ether-ethyl acetate solutions are combined and dried over anhydrous sodium sulfate and the solvents are removed by rotary evaporation to leave a light yellow solid, mp 123-126°C. Trituration of this material with 1:1 ethyl acetate-petroleum ether (Note 16) gives 7.9-8.0 g (61-62%) of cis-1-methylcyclopentane-1,2-dicarboxylic acid as a white solid, mp 123-124.5°C (Notes 16, 17, 18, and 19).

2. Notes

1. All glassware was dried overnight in an oven at 115°C and allowed to cool in a desiccator.

2. A slight positive pressure of nitrogen is maintained throughout the reaction.

3. A literature procedure² for the preparation of the zinc-copper couple was followed except for the use of slightly more (28%) than the indicated amount of copper sulfate. The checkers found that the kind of zinc used is critical. Zinc dust, 325 mesh, from Aldrich Chemical Company, Inc. [catalog number 20,998-8] gave 7,7-dichloro-1-methylbicyclo[3.2.0]heptan-6-one in 80-89% yield. Zinc metal (dust) from Fisher Scientific Company (Lot 874394) gave the dichloro ketone in yields of 37-61% (five trials). The Fisher zinc was of unknown mesh, but was much more finely-divided than the Aldrich Chemical Company, Inc. zinc.

4. Ether and tetrahydrofuran were distilled from the sodium ketyl of benzophenone.

5. 1-Methyl-1-cyclopentene (96% pure) and trichloroacetyl chloride (99% pure) were purchased from the Aldrich Chemical Company, Inc. The trichloroacetyl chloride was distilled prior to use.

6. Phosphorus oxychloride (99% pure) was obtained from the Aldrich Chemical Company, Inc. and distilled from potassium carbonate prior to use.

7. This material was found to darken with time. Its spectral properties are the following: IR (film) cm^{-1} : 1805; ^1H NMR (CDCl_3 , 80 MHz) δ : 1.57 (s, 3 H), 1.5-2.5 (m, 6 H), 3.50 (m, 1 H). These values are in accord with those in the literature.³

8. The solution of butyllithium in hexane was purchased from the Aldrich Chemical Company, Inc. and standardized with menthol and phenanthroline⁴ before use.

9. Acetic anhydride was distilled prior to use.

10. A trap is used between the flask and the rotary evaporator as a precaution against possible bumping during the evaporation.

11. Sodium periodate was obtained from the Aldrich Chemical Company, Inc. and ruthenium(III) chloride hydrate (5-10% water) was purchased from Fluka. The more expensive periodic acid can replace sodium periodate; however, ruthenium(III) chloride appears to be somewhat more efficient than ruthenium(IV) oxide.

12. Should a noticeably exothermic reaction ensue, the cooling bath is replaced for a few minutes.

13. At this point the checkers filtered the mixture through a pad of 30 g of Celite to remove the green precipitate. This filtration reduces the problem of emulsions and clogging of the separatory funnel during subsequent extractions.

14. Iodine formation becomes substantial at lower pH.

15. Normally 50-100 mL of this solution is required.

16. This is done first with 20 mL and then with 8 mL. Product loss is minimized by storing the trituration flask overnight at -25°C prior to removal of the supernatant solution. On evaporation, the supernatant solution affords an oil containing the diacid and a small amount of the corresponding anhydride. Treatment of this oil with 10% aqueous NaOH at room temperature overnight and then processing the solution as before yields an additional 0.4 g (3%) of the diacid, mp 126-127°C.

17. The submitters report a crude yield of 11.5 g (89%) and a recrystallized yield of 9.0 g (70%), mp 128-129°C.

18. Melting points from 123 to 129°C have been reported for this compound.⁵ Its spectral properties are the following: IR (Nujol) cm^{-1} : 2720, 2630, 1690; ^1H NMR (CDCl_3 , 80 MHz) δ : 1.44 (s, 3 H), 1.5-2.5 (m, 6 H), 2.72 (pseudo t, 1 H, $J = 0$), 10.0 (br s, 2 H).

19. Gas chromatographic analysis (10% Carbowax 20 M on 80-100 mesh Chromosorb W, 2.5 m x 2 mm, column temperature 180°C, injection temperature 230°C, flow rate 10 mL/min, retention time 10 min) of the corresponding dimethyl ester, formed with ethereal diazomethane, indicated a purity of greater than 99%.

3. Discussion

This procedure serves to illustrate a relatively inexpensive, two-pot, stereoselective method for effecting vicinal dicarboxylation of alkenes that is more generally applicable and higher-yielding than the palladium-catalyzed carbonylation reaction and other more circuitous procedures.⁶ Part A of this procedure is a slight modification of the dichloroketene-olefin cycloaddition method previously described by Krepski and Hassner.² Part B makes use of Sharpless and co-workers' ruthenium(III) chloride-catalyzed oxidation process⁷ for the cleavage of the β -chloro enol acetate, which is formed on trapping the β -chloro enolate intermediate with acetic anhydride. A slightly different, non-optimized version of this procedure has been used^{6,8} for the vicinal dicarboxylation of 1-decene, cis- and trans-2-butene, 2-methyl-2-butene, 2,3-dimethyl-2-butene, 1-methyl-1-cyclohexene, 1,6-dimethyl-1-cyclohexene, and 5 α -cholest-2-ene with overall yields of 52-83%.

cis-1-Methylcyclopentane-1,2-dicarboxylic acid has been previously prepared by a variety of methods: by oxidative cleavage (HNO_3) of cyclobutanone^{5a} and cyclopentanone^{5b} precursors, through saponification and oxidation (KMnO_4) of a γ -butyrolactone intermediate,^{5c} and by anhydride formation and then hydrolysis starting from mixtures of the cis and trans diacids (obtained in ca. 5 steps).^{5d,e} Compared with these methods, the cycloaddition-cleavage procedure is much more efficient and practical. It requires only readily available reagents and easily affords, without any chromatographic separations, a product of high purity.

1. Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité (LEDSS), Université Joseph Fourier de Grenoble, Bât. 52 Chimie Recherche BP. 68, 38402 Saint Martin d'Hères Cedex, France. This work was supported by CNRS (UA 332).
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

cis-1-Methylcyclopentane-1,2-dicarboxylic acid: 1,2-Cyclopentanedicarboxylic acid, 1-methyl-, cis-(±)- (10); (70433-31-7)

7,7-Dichloro-1-methylbicyclo[3.2.0]heptan-6-one: Bicyclo[3.2.0]heptan-6-one,

7,7-dichloro-1-methyl- (9); (51284-43-6)

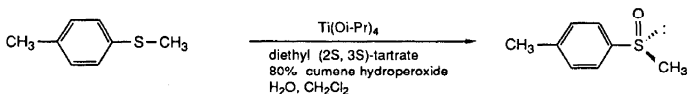
1-Methyl-1-cyclopentene: Cyclopentene, 1-methyl- (8,9); (693-89-0)

Trichloroacetyl chloride: Acetyl chloride, trichloro- (8,9); (76-02-8)

Sodium periodate: Periodic acid, sodium salt (8,9); (7790-28-5)

Ruthenium(III) chloride hydrate: Ruthenium chloride, hydrate (8,9); (14898-67-0)

ENANTIOSELECTIVE OXIDATION OF A SULFIDE:
(S)-(-)-METHYL p-TOLYL SULFOXIDE
(Benzene, 1-methyl-4-(methylsulfinyl)-, (S)-)



Submitted by S. H. Zhao, O. Samuel, and H. B. Kagan.¹

Checked by Carl A. Busacca and Albert I. Meyers.

1. Procedure

Into a 1-L flask containing 125 mL of methylene chloride (Note 1) and a magnetic stirring bar (4-cm length) is added at room temperature (20°C) 5.35 mL, 6.19 g (0.030 mol) of (S,S)-(-)-diethyl tartrate (DET) (Note 2) by means of a 10-mL syringe. The flask is stoppered with a septum cap and purged with argon. Titanium(IV) isopropoxide, Ti(OiPr)_4 , (4.48 mL, 0.015 mol) (Note 3) is introduced through the septum via a 10-mL syringe. The stirred limpid solution immediately turns yellow. After a few minutes distilled water (0.27 mL, 0.015 mol) is added dropwise using a calibrated syringe. Strong stirring is maintained until there is total dissolution of water and formation of a pale yellow solution (after 25 min). Methyl p-tolyl sulfide (4.09 mL, 4.20 g, 0.030 mol) (Note 4) dissolved in 5 mL of methylene chloride is introduced with a 10-mL syringe which is then rinsed with 5 mL of methylene chloride. The flask is cooled (-30°C) with an acetone-dry ice bath while it is stirred for

40 min. At this point 5.54 mL of 80% cumene hydroperoxide (Note 5) (0.030 mol, 5.70 g) is added dropwise from a 10-mL syringe, with stirring, during 5 min. The reaction flask is kept in a freezer (-23°C) overnight (15 hr) (Note 6). Hydrolysis is then effected by adding 5.05 mL of water followed by vigorous stirring for 90 min at room temperature (20°C).

A large sintered-glass funnel (9-cm diameter, porosity grade 2) is partially filled with Celite (Celite height: 2.5 cm) and then impregnated with methylene chloride. The suspension resulting from hydrolysis is poured in portions onto the Celite under suction by a water pump. The Celite is washed many times with 50-mL portions of technical-grade methylene chloride. In order to accelerate filtration and to improve washing, the surface of the Celite is disturbed from time to time with a spatula. The filtration time is approximately 50 min. The filtrate (300 mL) is then vigorously stirred for 1 hr in a mixture of 80 mL of 2 N sodium hydroxide and 40 mL of saturated aqueous sodium chloride. The organic phase [negative test for peroxides using a Merck kit (Merckoquant 10011)] is decanted, dried (magnesium sulfate or sodium sulfate), filtered and concentrated in a Büchi apparatus (bath temperature: 45°C) to leave 10 g of an oily material which is a mixture of methyl p-tolyl sulfoxide, 2-phenyl-2-propanol, and some starting sulfide. Optically pure sulfoxide is then easily isolated as follows:

The crude product (10 g) is diluted with 4 mL of a solvent mixture (ethyl acetate/cyclohexane = 9:1). This solution is poured onto a column (75-mm diameter) filled with 120 g of silica gel (Merck 230-400 mesh) for flash chromatography. Elution is performed under gravity and requires ~200 mL of the above solvent system, followed by ~200 mL of ethyl acetate. 2-Phenyl-2-propanol mixed with methyl p-tolyl sulfide is eluted in the first fraction (~150 mL, monitored by TLC). The subsequent fractions are collected (~300 mL)

and evaporated, giving 4.0 g of methyl p-tolyl sulfoxide $[\alpha]_D -88^\circ$ (acetone, c 1), 89% ee, 85% yield. This material is crystallized once from 60 mL of hot hexane. to afford, after 2 hr at 20°C , 3.14 g (68%) of enantiomerically pure (Note 7) (S)-(-)-methyl p-tolyl sulfoxide as needles, $[\alpha]_D -142^\circ$ (acetone, c 1), mp $73-76^\circ\text{C}$ (Reichert microscope with heating system).

The chemical purity of the compound is checked by ^1NMR (250 MHz) and thin layer chromatography (silica gel, eluent: ethyl acetate) which show the complete absence of the corresponding sulfide and sulfone (Note 8).

2. Notes

1. Methylene chloride, technical grade (99.5%), was passed through a column of basic alumina (grade I) and then stored over molecular sieves (4 \AA).

2. (-)-Diethyl (S,S)-tartrate was obtained from the Aldrich Chemical Company, Inc. and was distilled (bp $120^\circ\text{C}/2 \text{ mm}$).

3. Titanium(IV) isopropoxide, $\text{Ti}(\text{OiPr})_4$ (Aldrich Chemical Company, Inc.) was distilled under an inert atmosphere (nitrogen or argon) and stored in a flask with a septum cap under argon (bp $85^\circ\text{C}/1.5 \text{ mm}$).

4. Methyl p-tolyl sulfide, available from Aldrich Chemical Company, Inc., was distilled (bp 95°C , 18 mm) before use.

5. Cumene hydroperoxide, obtained from Aldrich Chemical Company, Inc., technical grade (80%), was dried overnight over 4 \AA molecular sieves (pellets) prior to use.

6. A standard freezer without accurate temperature control was used; it is estimated that the temperature is $-23^\circ\text{C} \pm 1^\circ\text{C}$. One night is a convenient reaction time, but oxidation is in fact complete after a few hours.

7. Enantiomerically pure (R)-(+)-methyl p-tolyl sulfoxide, prepared from (-)-menthyl p-tolylsulfinate,²⁻⁴ was described with the following specific rotations: $[\alpha]_D^{25} +145.5^\circ$ (acetone),³ $[\alpha]_D^{25} +168^\circ$ (acetone, c 1.8),⁴ $[\alpha]_D +189^\circ$ (CHCl_3 , c 1).⁵ The submitters checked a sample prepared^{3,4} and kindly provided by Professor G. Solladié (Strasbourg), which was recrystallized from hexane: $[\alpha]_D +146^\circ \pm 1$ (acetone, c 1), mp 76-77°C. HPLC analysis carried out on a chiral stationary phase shows the absence of the enantiomer (Dr. Tambute, private communication). The same analysis shows that the product obtained by the procedure described above is of 99.5% ee.

8. The checkers attempted chromatography of the three-component mixture on a 150-mmol scale using 55- and 75-mm diameter columns. However, mixed fractions were obtained even with seemingly large R_f differences for the components.

3. Discussion

Both enantiomers of methyl p-tolyl sulfoxide are available from the above procedure by selection of the appropriate diethyl tartrate. This procedure describes the preparation of (S)-(-)-methyl p-tolyl sulfoxide which is not easy to prepare by the Andersen method²⁻⁴ using (+)-menthol.

Cumene hydroperoxide was selected because it was recently observed⁶ that it gives in many cases better ee's in asymmetric oxidation of sulfides than the original procedure with t-butyl hydroperoxide.⁷⁻⁹

The enantiomeric purity of the crude (S)-methyl p-tolyl sulfoxide produced from the oxidation is close to 90% (measurement made on a sample of 200 mg of material purified by flash chromatography on silica gel, eluent: ethyl acetate - ethanol = 96:4). However, when oxidation is performed on a

10-mmol scale, enantioselectivity is improved (96% ee, 87% isolated yield).⁶ We have no explanation for this optimum scale effect. It could be because of easier temperature control on a small scale (there is a decrease of enantioselectivity above -20°C or below -25°C).⁷

t-Butyl hydroperoxide (anhydrous toluene solution prepared as described in (9)) was also used as the oxidant on a 0.11-mol scale in the presence of 0.10 mol of methyl p-tolyl sulfide and 0.053 mol of chiral titanium complex (Ti/DET/H₂O = 1:2:1). The procedure is identical with the one described above using cumene hydroperoxide. The ee of the crude sulfoxide is 84%. Pure (S)-methyl p-tolyl sulfoxide [α]_D -146° (acetone, c 1) is obtained without flash chromatography by three recrystallizations of the crude material from hexane in 50% yield (with respect to sulfide).

Preparation of various enantiomerically pure sulfoxides by oxidation of sulfides seems feasible in the cases where asymmetric synthesis occurs with ee's in the range of 90% giving crystalline products which can usually be recrystallized up to 100% ee. Aryl methyl sulfides usually give excellent enantioselectivity during oxidation⁶⁻⁹ and are good candidates for the present procedure. For example, we have shown on a 10-mmol scale that optically pure (S)-(-)-methyl phenyl sulfoxide [α]_D -146° (acetone, c 1)⁶ could be obtained in 76% yield after oxidation with cumene hydroperoxide followed by flash chromatographic purification on silica gel and recrystallizations at low temperature in a mixed solvent (ether-pentane). Similarly (S)-(-)-methyl o-methoxyphenyl sulfoxide, [α]_D -339° (acetone, c 1.5 100% ee measured by HPLC), was obtained in 80% yield by recrystallizations from hexane.

The method with cumene hydroperoxide has been recently used with success,¹⁰ to prepare both enantiomers of methyl p-methoxyphenyl sulfoxide which were then taken as starting material for the total synthesis of biological compounds.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(-)-Methyl p-tolyl sulfoxide: Benzene, 1-methyl-4-(methylsulfinyl)-, (S)- (9); (5056-07-5)

(S,S)-(-)-Diethyl tartrate: Tartaric acid, diethyl ester, (-)- or D- (8):

Butanedioic acid, 2,3-dihydroxy-, diethyl ester, [S-(R*,R*)]- (9);
(13811-71-7)

Titanium(IV) isopropoxide: Isopropyl alcohol, titanium(4+) salt (8):

2-Propanol, titanium(4+) salt (9); (546-68-9)

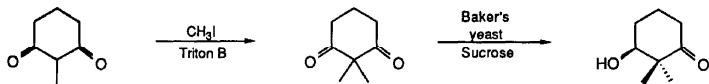
Methyl p-tolyl sulfide: Sulfide, methyl p-tolyl (8); Benzene, 1-methyl-4-(methylthio)- (9); (623-13-2)

Cumene hydroperoxide: Hydroperoxide, α,α -dimethylbenzyl (8); hydroperoxide, 1-methyl-1-phenylethyl (9); (80-15-9)

YEAST REDUCTION OF 2,2-DIMETHYLCYCLOHEXANE-1,3-DIONE:

(S)-(+)-3-HYDROXY-2,2-DIMETHYLCYCLOHEXANONE

(Cyclonexanone, 3-hydroxy-2,2-dimethyl-, (S)-)



Submitted by Kenji Mori and Hideto Mori.¹

Checked by Mark Hopkins and Larry E. Overman.

1. Procedure

A. *2,2-Dimethylcyclohexane-1,3-dione*. In a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, 200-mL, pressure-equalizing dropping funnel and reflux condenser (the top of which is connected to a calcium chloride drying tube) are placed 50.4 g (0.4 mol) of 2-methylcyclohexane-1,3-dione² and 500 mL of dry methanol. To this stirred solution is added dropwise 168 mL of commercial Triton B (40% in methanol) (Notes 1 and 2). After the addition is complete, the resulting solution is stirred at room temperature for 10 min and 60.0 g (0.423 mol) of methyl iodide is added portionwise. This solution is then stirred and heated under reflux for 16-20 hr (Note 3). After the reaction mixture is cooled to room temperature, about 400 mL of methanol is removed by rotary evaporation. The residue is poured into a mixture of 100 mL (1.2 mol) of concd hydrochloric acid and about 100 g of ice to decompose the O-alkylated product (Note 4), and the mixture is stirred for 30 min. The precipitated solid (recovered starting material) is

collected by filtration and the filtrate is extracted four times with 100 mL of ethyl acetate. The combined ethyl acetate extracts are washed with 5% sodium thiosulfate solution (4 x 100 mL), saturated sodium hydrogen carbonate solution (2 x 100 mL) and saturated sodium chloride solution (100 mL), dried over anhydrous magnesium sulfate and filtered. Ethyl acetate is removed by rotary evaporation and the residue is distilled to give 30-32 g (54-57%) of 2,2-dimethylcyclohexane-1,3-dione, bp 92-97°C (4 mm) as a glassy solid (Notes 5 and 6).

B. *(S)-(+)-5-Hydroxy-2,2-dimethylcyclohexanone*. In a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and stopper are placed 3 L of tap water and 450 g of sucrose (Note 7). The mixture is stirred at 30°C, and 200 g of dry baker's yeast (Note 8) is added with stirring, whereupon brisk fermentation takes place (Note 2). This fermenting mixture is stirred at 30°C for 10 min and a solution of 15 g (0.107 mol) of 2,2-dimethylcyclohexane-1,3-dione in 95% ethanol (30 mL) and 0.2% Triton X-100 (120 mL) is added portionwise (Note 9). The mixture is stirred at 30°C for 40-48 hr (Note 10). Diethyl ether (about 200 mL) and Celite (about 50 g) are then added to the mixture and it is left to stand overnight. After the flocculated yeast cells are precipitated, the mixture is filtered through a pad of Celite (Note 11). The filter-cake is washed with ethyl acetate (2 x 100 mL) and the combined filtrate and washings are saturated with sodium chloride and extracted four times with 100 mL of ethyl acetate. The combined ethyl acetate extracts are washed with saturated sodium hydrogen carbonate solution (200 mL) and saturated sodium chloride solution (200 mL), dried over anhydrous magnesium sulfate and filtered. Ethyl acetate is removed by rotary evaporation and the residue (about 20 g) is chromatographed over 200 g of silica gel (Fuji Davison 820 MH gel) (Note 12).

Elution with hexane-ethyl acetate (10:1-5:1) gives 5-6 g of recovered starting material. Further elution with hexane-ethyl acetate (5:1-1:2) gives 7.7-7.9 g (47-52%) of (S)-3-hydroxy-2,2-dimethylcyclohexanone. An analytical sample can be obtained by distillation, bp 85-87°C/3.7 mm, $[\alpha]_D^{21} +23.0^\circ$ (CHCl₃, c 2.0) (Notes 13, 14, and 15).

2. Notes

1. The submitters used Triton B purchased from Tokyo Kasei Co., Ltd. whereas the checkers used material purchased from Aldrich Chemical Company, Inc.

2. No temperature control is required because of the non-exothermic nature of this reaction.

3. The checkers found (GLC analysis using a 12.5-m, 5% methyl silicone capillary column) that the reaction was complete within 4-6 hr.

4. To ensure the complete decomposition of the O-alkylated product, this amount of hydrochloric acid is used. A smaller amount may result in incomplete decomposition of the by-product.

5. This material is sufficiently pure for use in the next step. Analysis by ¹³C NMR indicates that 2-4% of an unknown impurity is present. Recrystallization from hexane-methylene chloride gives pure product melting at 37-38°C

6. The spectra are as follows: ¹H NMR (250 MHz, CDCl₃) δ: 1.29 (s, 6 H), 1.93 (5 lines, 2 H, J = 6.5), 2.67 (t, 4 H, J = 6.9); ¹³C NMR (76 MHz, CDCl₃) δ: 18.1, 22.3, 37.4, 61.8, 210.6.

7. Commercially available sucrose is used. The checkers employed deionized water.

8. The submitters used yeast purchased from the Oriental Yeast Co., Ltd., whereas the checkers used Fleischman's Dry Active Yeast.

9. The submitters used Triton X-100 purchased from Tokyo Kasei Co., Ltd. whereas the checkers used material purchased from Rohm & Haas Co.

10. To keep the temperature at 30°C, the flask is gently heated on a large water bath.

11. The checkers found that the use of coarse filter paper and a Buchner funnel was preferable to a sintered glass funnel.

12. The checkers found that the chromatography was best accomplished using 450 g of silica gel (E. Merck).

13. The spectral properties of (S)-(+)-3-hydroxy-2,2-dimethylcyclohexanone are as follows: IR ν_{max} (film) cm^{-1} : 3470 (s), 1705 (s), 1120 (m), 1055 (s), 985 (s), 965 (m); ^1H NMR (250 MHz, CDCl_3) δ : 1.11 (s, 3 H), 1.15 (s, 3 H), 1.60-1.71 (m, 1 H), 1.76-1.86 (m, 1 H), 1.96-2.05 (m, 2 H), 2.16 (br s, 1 H), 2.35-2.45 (m, 2 H), 3.69 (dd, 1 H, $J = 7.6, 2.9$); ^{13}C NMR (76 MHz, CDCl_3) δ : 19.7, 20.7, 22.9, 29.0, 37.3, 51.3, 77.8, 215.3.

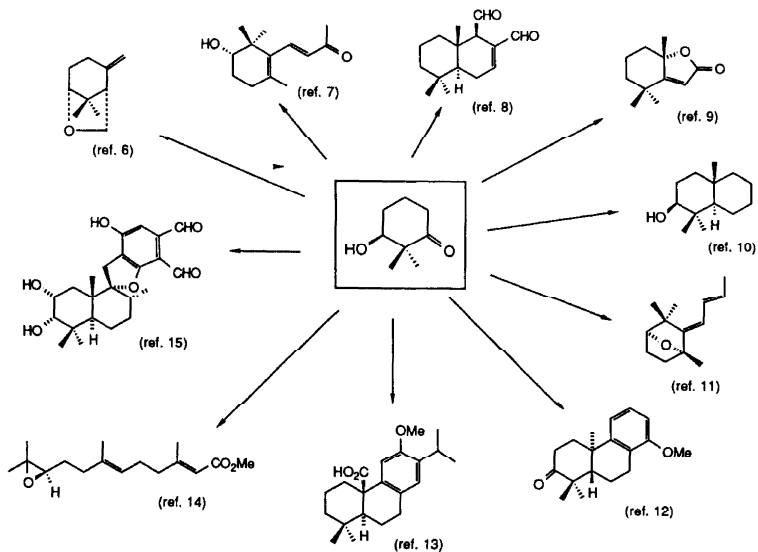
14. The optical purity of (S)-(+)-3-hydroxy-2,2-dimethylcyclohexanone can be determined by HPLC analysis. The (S)- α -methoxy- α -trifluoromethylphenylacetate (MTPA ester) is prepared according to the reported procedure:³ HPLC analysis (Column, Nucleosil® 50-5, 25 cm x 4.6 mm; eluent, hexane:THF = 30:1, 1.03 mL/min; detected at UV 256 nm) retention time 25.6 min (98.0-99.4%) and 29.6 min (0.6-2.0%). Therefore the optical purity is determined to be 96.0-98.8% ee.

15. Analysis of the MTPA ester of this product by 250 MHz ^1H NMR and capillary GLC (12.5 m, 5% methyl silicone column) failed to detect any more of the minor diastereomer than would have been expected from the purity (98% ee) of the MTPA-Cl employed.

3. Discussion

Microbial reduction of prochiral cyclopentane- and cyclohexane-1,3-diones was extensively studied during the 1960's in connection with steroid total synthesis.⁴ Kieslich, Djerassi, and their coworkers reported the reduction of 2,2-dimethylcyclohexane-1,3-dione with *Kloeckera magna* ATCC 20109, and obtained (S)-3-hydroxy-2,2-dimethylcyclohexanone.⁵ We found that the reduction of the 1,3-diketone can also be effected with conventional baker's yeast, and secured the hydroxy ketone of 98-99% ee as determined by an HPLC analysis of the corresponding (S)- α -methoxy- α -trifluoromethylphenylacetate (MTPA ester).^{6,7} (S)-3-Hydroxy-2,2-dimethylcyclohexanone has been proved to be a versatile chiral non-racemic building block in terpene synthesis as shown in Figure 1.

Figure 1. Natural Products Synthesized from
(S)-3-Hydroxy-2,2-dimethylcyclohexanone



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone: Cyclohexanone, 3-hydroxy-2,2-dimethyl-, (S)- (11); (87655-21-8)

2,2-Dimethylcyclohexane-1,3-dione: 1,3-Cyclohexanedione, 2,2-dimethyl- (8,9); (562-13-0)

2-Methylcyclohexane-1,3-dione: 1,3-Cyclohexanedione, 2-methyl- (8,9); (1193-55-1)

Triton B: Ammonium, benzyltrimethyl-, hydroxide (8); Benzenemethanaminium, N,N,N-trimethyl-, hydroxide (9); (100-85-6)

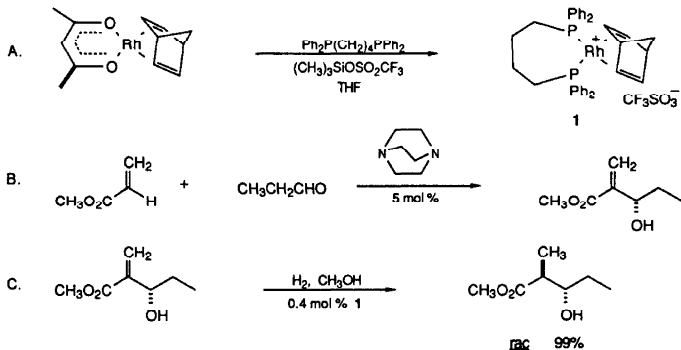
Sucrose (8); α -D-Glucopyranoside, β -D-fructofuranosyl (9); (57-50-1)

Triton X-100: Glycols, polyethylene, mono[p-(1,1,3,3-tetramethylbutyl)-phenyl]ether (8); Poly(oxy-1,2-ethanediyl), α -[4-(1,1,3,3-tetramethylbutyl)-phenyl]- ω -hydroxy- (9); (9002-93-1)

DIRECTED HOMOGENEOUS HYDROGENATION: METHYL

anti-3-HYDROXY-2-METHYLPENTANOATE

(Pentanoic acid, 3-hydroxy-2-methyl-, methyl ester, (*R*,R**)-(*±*)-)



Submitted by John M. Brown, Phillip L. Evans, and Alun P. James.¹

Checked by Ulrike Eggert, H. M. R. Hoffmann, and Ekkehard Winterfeldt.

1. Procedure

A. *Bicyclo[2.2.1]hepta-2,5-diene 1,4-bis(diphenylphosphino)butane-rhodium trifluoromethanesulfonate, 1.* A 250-mL, two-necked, round-bottomed flask equipped with a septum, two-way stopcock used as a gas inlet and outlet, and a magnetic stirrer is charged with a solution of bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorrhodium (117.6 mg, 0.4 mmol) (Note 1) in dry tetrahydrofuran (2.5 mL) under a gentle stream of argon. Trimethylsilyl

trifluoromethanesulfonate (97.8 mg, 0.44 mmol) (Note 2) is added in one portion by microsyringe via the septum, resulting in a color change from yellow to orange. Solid 1,4-bis(diphenylphosphino)butane (170.4 mg, 0.4 mmol) (Note 3) is added all at once, with removal and immediate replacement of the septum cap. The color of the solution darkens to a deep orange-red, and precipitation of an orange solid occurs over 1-2 min. Dry 30-40 petroleum ether (10 mL) is added with vigorous stirring. The mixture is allowed to settle and the solvent is removed first by syringe and finally under reduced pressure with an oil pump. Argon is admitted and the catalyst is dried and stored under argon (Notes 4, 5).

B. Methyl 3-hydroxy-2-methylenepentanoate. A 250-mL, round-bottomed flask is charged with methyl acrylate (50.0 mL, 0.556 mol), propionaldehyde (60.0 mL, 0.832 mol), and 1,4-diazabicyclo[2.2.2]octane (3.0 g, 26.8 mmol) (Note 6). After the solution is stirred briefly to ensure complete dissolution, the flask is stoppered and set aside at ambient temperature for 7 days. The reaction mixture is then dissolved in dichloromethane (150 mL), washed with 1 M hydrochloric acid (100 mL), and the organic layer is separated and dried over anhydrous magnesium sulfate. Solvent is removed under reduced pressure after filtration and the residue is fractionated through a 12"-vacuum-jacketed Vigreux column. The main fraction boiling at 54°C (0.1 mm) is collected as a water-white liquid to afford 57 g (71%) of condensation product (Note 7). Care must be taken in the distillation to avoid contamination by high-boiling impurities which may inactivate the catalyst.

C. Methyl dl-anti-3-hydroxy-2-methylpentanoate. Freshly distilled methyl 3-hydroxy-2-methylenepentanoate (14.4 g, 0.1 mol) is added to the biphosphinorhodium catalyst (catalyst/substrate ratio 1/250) (Note 8) in the flask from step A. Methanol (40 mL, distilled from $\text{Mg}(\text{OMe})_2$) is added. The

apparatus is sealed with a rubber septum, the side-arm is connected to a burette line, and the apparatus is then transferred to a dry ice/2-propanol bath. The vessel is evacuated to 1 mm three times and filled with hydrogen (Note 9) each time, the burette being partially filled on the last occasion. The mixture is warmed to near ambient temperature and transferred to a water bath at $12 \pm 2^\circ\text{C}$ (Note 10). When thermal equilibration is complete, the stirrer is started so as to create a deep vortex in the reaction solution, which darkens to a brick-red color with rapid uptake of hydrogen. The burette is recharged with hydrogen as necessary, and gas absorption occurs steadily until the reaction is complete, when ca. 2.5 L of hydrogen has been consumed (Note 11). Completion of reaction can readily be checked by addition of 50 μL of methyl 3-hydroxy-2-methylenepentanoate to the reaction solution by microsyringe, leading to a perceptible burst of gas absorption. At this stage the flask is disconnected from the hydrogen line, flushed with argon and the contents are transferred to a 250-mL, round-bottomed flask. Solvent is removed at ambient temperature on a rotary evaporator, and the residue is dissolved in diethyl ether (40 mL) and 30-40 petroleum ether (150 mL). The mixture is filtered through a small plug of silica (60 μ , Merck flash chromatography grade) which effectively retains the residual rhodium catalyst (Note 1). Solvents are removed on a rotary evaporator, and the colorless product (Note 12) is distilled in a Kugelrohr apparatus, bp 50°C (~ 0.5 mm). The yield of methyl dl-anti-3-hydroxy-2-methylpentanoate is 13.3 g (91%), chemically and stereochemically pure by ^{13}C NMR (Note 13).

This procedure may be adapted for kinetic resolution of the reactant, employing an optically active biphosphinerhodium catalyst (Note 13).

2. Notes

1. The starting material for complex preparation is $\text{RhCl}_3 \cdot 3 \text{H}_2\text{O}$, obtained as a loan from Johnson Matthey Co. Rhodium-containing reaction residues are collected for return. The synthesis of bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorrhodium has been described by Wilkinson,² and later by Green,² and may be carried out by the following modification: $\text{RhCl}_3 \cdot 3 \text{H}_2\text{O}$ (0.68 g, 2.58 mmol) was dissolved in 90% ethanol (10 mL) and stirred with freshly distilled bicyclo[2.2.1]hepta-2,5-diene (1.95 mL) for 2 days under argon. The yellow precipitate was filtered, dried and dissolved in tetrahydrofuran (10 mL) to which was added sodium 2,4-pentanedionate (0.314 g, 2.58 mmol) in one portion. The suspension was stirred vigorously for 4 hr, filtered and solvent removed from the filtrate under reduced pressure. The resulting complex [530 mg, 70%, mp 172-175°C (lit.² 175-177°C)] is sufficiently pure to use, but may be sublimed under reduced pressure if desired. Alternatively, catalysts may be purchased from Chemical Products, Johnson Matthey Co., Royston, Cambridgeshire, England.

2. This toxic and corrosive reagent (Aldrich Chemical Company, Inc.) was transferred directly from the septum-sealed commercial sample.

3. This reagent was obtained from the Strem Chemical Company, Inc.

4. If it is desired to isolate and store the catalyst, an alternative procedure, preferred by the submitters, may be used. A 25-mL Schlenk tube is used as a reaction flask. After addition of the petroleum ether, the resulting orange suspension is filtered by centrifugation in a Craig tube and dried under argon. The bright orange solid (0.26-0.28 g), mp 211-212°C (dec), is indefinitely stable when stored in a -20°C freezer under argon.

5. Earlier work on directed hydrogenation used tetrafluoroborate salts.³ Triflate salts seem superior in keeping properties, and their preparation is easy and convenient.

6. Methyl acrylate, 99% (stabilized with 200 ppm hydroquinone monomethyl ether), propionaldehyde 97%, and 1,4-diazabicyclo[2.2.2]octane were purchased from the Aldrich Chemical Company, Inc. and used as supplied.

7. The Michael-induced condensation reaction between acrylates and aldehydes⁴ is dramatically accelerated by high pressure, cutting the reaction time from several days to a few minutes.⁵

8. The submitters used a 1:500 catalyst/substrate ratio, (H_2 uptake ca. 40 mL/min) but the checkers used the higher ratio to speed up the hydrogen uptake. If an accurate rate of hydrogen uptake is crucial to a user, the lower ratio may be preferred.

9. Hydrogen of 99.99% purity, supplied by the British Oxygen Company, was employed.

10. The diastereoselectivity of reduction increases with decreasing temperature, and the conditions chosen represent a compromise between rate and specificity.

11. On one occasion the submitters added an extra 15.0 g of starting material to the reaction vessel at this point. Hydrogenation proceeded to completion (i.e., 1000 turnovers, in total) but slowed appreciably in the latter stages of reaction.

12. The submitters fractionated the product through a short Vigreux column, collecting the main fraction boiling at 65°C (1 mm). The ^{13}C NMR spectrum of the bulk reaction product is as follows: ($CDCl_3$) δ : 8.89 (CH_3CH), 13.19 (CH_3CH_2), 26.41 (CH_2), 44.21 (OCH_3), 50.79 ($CH-CO$), 73.73 ($CH-O$), 175.63 ($C=O$). The syn isomer exhibits resonances at ($CDCl_3$) δ : 9.10, 13.19, 28.33,

44.21, 50.94, 71.53; it may be prepared by Pd/C/H₂ reduction of the starting material and separation of the diastereomers of product by preparative GLC (OV 225, 15', 150°C).

13. When (R,R)-1,2-bis(o-anisylphenylphosphino)ethanerhodium triflate (DIPAMPRh⁺) was used as catalyst,⁶ 5.0 g of starting material was hydrogenated with 0.1 g of catalyst in methanol at 0°C to 65% reaction (ca. 6 hr). Workup and isolation by preparative GLC (OV 225, 15', 150°C) gave 2.0 g of 2R,3R-(-)-methyl 3-hydroxy-2-methylpentanoate, [α]_D²⁰₅₈₇ -6.4° (chloroform, c 4) and 0.8 g of recovered S-(-)-methyl 3-hydroxy-2-methylenepentanoate, [α]_D²⁰₅₈₇ -20.3° (chloroform, c 2). The optical purity of the former is 57 ± 2% by chiral shift NMR (Eu(hfc)₃) and the latter is ≥ 97% optically pure. This represents an enantiomer ratio of 13:1.

3. Discussion

α-Substituted β-hydroxy esters are the formal product of an ester enolate aldol condensation. High anti-stereoselectivity in the reaction requires the lithium enolate of a reasonably bulky aryl ester and a sterically demanding aldehyde. The condensation between 2,6-dimethylphenyl propionate and 2-methylpropanal has been described in *Organic Syntheses*,⁷ under conditions where the product is formed with 98% anti-selectivity. Recently the condensation of E-silylketene acetals derived from N-methylephedrine esters with aldehydes mediated by titanium(IV) chloride has been shown to occur with good anti-selectivity and in high ee.⁸

Alternatively, the anti-α-alkyl-β-hydroxy ester structure may be obtained by alkylation of the dianion of a β-hydroxy ester, which occurs with ≥ 95% stereoselectivity.⁹ Since the starting materials are available in moderate to

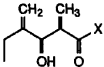
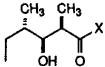
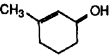
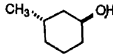
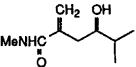
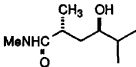
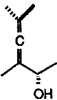
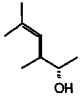


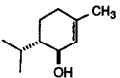
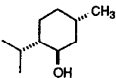
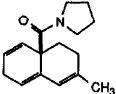
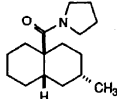
high optical purity by yeast reduction of β -keto esters, ^{10a,b} this constitutes an asymmetric synthesis.^{10c}

The present procedure involving homogeneous catalysis is operationally simple and takes advantage of the easy availability of 2-(1'-hydroxyalkyl)-acrylic esters. A two-step procedure involving kinetic resolution of the racemic starting material with an optically active hydrogenation catalyst, followed by a further reduction with an achiral catalyst, leads to diastereomerically pure products in $\geq 97\%$ ee.

Directed hydrogenation is applicable to olefins which are α' -disubstituted or trisubstituted with a polar functional group at an adjacent chiral center.¹¹ The latter must be capable of sustained coordination to the metal during the catalytic cycle, thereby exerting stereochemical control on hydride transfer to carbon. The presence of an electron-withdrawing group at the α' -position enhances both the reaction rate and stereoselectivity, making 2-(1'-hydroxyalkyl)acrylates highly suitable substrates for the reaction. The polar group is most commonly -OH, but CO_2Me , CONR_2 , NHCOR and NHCO_2R have all been used. Other substituents including OMe , OCOR and NH_2 are much less effective. For acyclic cases where the reactant possesses conformational flexibility, cationic rhodium complexes derived from the 7-ring chelate of 1,4-bis(diphenylphosphino)butane have proved most effective. With cyclic reactants cationic iridium catalysts of the type introduced by Crabtree and Morris¹² have generally been more successful, and the procedure is more tolerant of steric bulk in the reactant olefin. A series of examples is collected in Table I.

Substituted acrylates (which resemble the enamide substrates employed in asymmetric hydrogenation)¹³ may be deracemized by reduction with an optically active catalyst, especially DIPAMPRh⁺. Selectivity ratios of 12:1 to 22:1 have been obtained for a variety of reactants; with compounds of reasonable volatility, separation of starting material and product may be effected by preparative GLC. Recovered starting material can then be reduced with an achiral catalyst to give the optically pure anti product. Examples of kinetic resolutions by this method are given in Table II. More recently very successful kinetic resolutions of allylic alcohols have been carried out with Ru(BINAP) catalysts.^{10c}

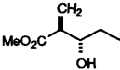
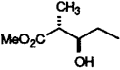
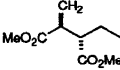
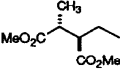
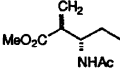
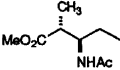
TABLE I
Directed Homogeneous Hydrogenation

Reactant	Product	Catalyst ^a (mol %)	Selectivity
		A (>2)	93 ^{3b}
		A (20)	99.6 ^{3b}
		A (2)	92 ³
		A (3)	97 ³
		B (20)	96 ¹⁴
		B (2.5)	99.7 ¹⁵
		B (5)	99.9 ¹⁵

^aCatalyst A is complex 1 (see text); catalyst B is (PCx₃)(py)(C₈H₁₂)IrPF₆.

TABLE II

Kinetic Resolutions in Acrylate Hydrogenation^a

Recovered reactant	Major product	% Reaction	Ee
		65	98 ¹³
		65	96 ¹⁷
		58	96 ¹⁸

^a 1-4 mol % DIPAMPRh⁺ in MeOH, usually at 0°C.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

Methyl anti-3-hydroxy-2-methylpentanoate: Pentanoic acid, 3-hydroxy-2-methyl, methyl ester, (R*,R*)-(±)- (11); (100992-75-4)

Bicyclo[2.2.1]hepta-2,5-diene-1,4-bis(diphenylphosphino)butanerhodium trifluoromethanesulfonate: Rhodium(1+), [(2,3,5,6-)-bicyclo[2.2.1]hepta-2,5-diene][1,4-butanediylbis[diphenylphosphine]-P,P']-, trifluoromethanesulfonate

Bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorhodium: Rhodium, (2,5-norbornadiene) (2,4-pentanedionato)- (8); Rhodium, [(2,3,5,6-)-bicyclo[2.2.1]hepta-2,5-diene] (2,4-pentanedionato-0,0')- (9); (32354-50-0)

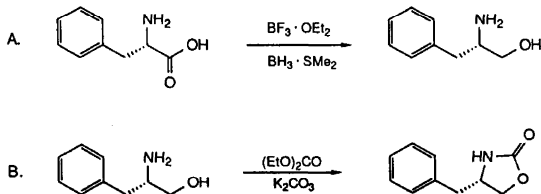
Trimethylsilyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, trimethylsilyl ester (8,9); (27607-77-8)

1,4-Bis(diphenylphosphino)butane: Phosphine, tetramethylenebis[diphenyl]- (8); Phosphine, 1,4-butanediylbis[diphenyl]- (9); (7688-25-7)

Methyl 3-hydroxy-2-methylenepentanoate: Pentanoic acid, 3-hydroxy-2-methylene-, methyl ester (9); (18052-21-6)

1,4-Diazabicyclo[2.2.2]octane (8,9); (280-57-9)

(S)-4-(PHENYLMETHYL)-2-OXAZOLIDINONE
(2-Oxazolidinone, 4-(phenylmethyl)-, (S)-)



Submitted by James R. Gage and David A. Evans.¹

Checked by Philip G. Meister and Leo A. Paquette.

1. Procedure

Caution! This reaction should be carried out in a hood since dimethyl sulfide is liberated during the course of the reaction.

A. *(S)*-Phenylalanol. A dry, 3-L, three-necked flask is equipped with a mechanical stirrer and a reflux condenser connected to a mineral oil bubbler. The flask is loaded with 165 g (1.00 mol) of (*S*)-phenylalanine (Note 1), then equipped with a 250-mL pressure-equalized addition funnel capped with a rubber septum through which is inserted a nitrogen-inlet needle. The flask is swept with nitrogen and filled with 500 mL of anhydrous tetrahydrofuran, and the addition funnel is charged with 123 mL (1.00 mol) of freshly distilled boron trifluoride etherate via cannula (Note 2). The boron trifluoride etherate is added dropwise to the phenylalanine slurry over a 30-min period with stirring, and the mixture is heated at reflux for 2 hr, resulting in a

colorless, homogeneous solution. The addition funnel is then charged via cannula with 88 g (110 mL, 1.15 mol) of 10 M borane-dimethyl sulfide complex (Note 3), which is added carefully to the *vigorously* refluxing solution over a 100-min period. During the course of the addition there is continuous evolution of dimethyl sulfide and hydrogen gas, and the solution turns from orange to light brown. A vigorous exotherm occurs approximately halfway through the addition period. (*Caution!* Note 4). The solution is heated at reflux for an additional 6 hr after the addition is complete (Notes 5 and 6), then allowed to cool to ambient temperature. The excess borane is quenched by the slow addition of 125 mL of a 1:1 tetrahydrofuran-water solution followed by 750 mL of 5 M aqueous sodium hydroxide. The resulting two-phase mixture is heated at reflux for 12 hr, cooled to room temperature, and filtered through a coarse fritted funnel. The residual solids are washed with two 25-mL portions of tetrahydrofuran, and the filtrate is concentrated on a rotary evaporator to remove the bulk of the tetrahydrofuran. The resulting slurry is extracted with one 400-mL and three 200-mL portions of dichloromethane. The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation, yielding 141-158 g (93-104%) of a white crystalline solid which is recrystallized from ca. 600 mL of ethyl acetate to give 111-113 g (73-75%) of the desired product as white needles in two crops, mp 88.5-91°C (Note 7).

B. (*S*)-4-(*Phenylmethyl*)-2-oxasolidinone. A dry, 1-L, three-necked flask is equipped with a mechanical stirrer and a 12-in Vigreux column fitted with a distillation head and 200-mL receiver flask connected to a nitrogen source and bubbler. The flask is charged with 151 g (1.00 mol) of (*S*)-phenylalanol, 13.8 g (0.100 mol) of anhydrous potassium carbonate, and 250 mL (2.06 mol) of diethyl carbonate (Note 8). The mixture is lowered into an oil bath,

preheated to 135°C, and is stirred until dissolution is achieved (ca. 5 min). The distillation receiver is cooled in an ice bath, and ca. 120 mL of ethanol is collected from the reaction over a 2.5-hr period. The oil bath is removed upon cessation of the ethanol distillation. After the light yellow solution is cooled to ambient temperature, it is diluted with 750 mL of dichloromethane, transferred to a separatory funnel, and washed with 750 mL of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotary evaporator affording 200 g (113%) of a white crystalline solid. This material is taken up into 600 mL of a hot 2:1 ethyl acetate-hexane solution, filtered while hot, then allowed to crystallize to afford 136-138 g (78-79%) of large white plates, mp 84.5-86.5°C (Notes 9 and 10).

2. Notes

1. (S)-Phenylalanine was obtained by the submitters from Ajinomoto Company, Inc. The starting material obtained by the checkers from Sigma Chemical Company was dried under reduced pressure over phosphorus pentoxide for 2 days.

2. Reagent grade tetrahydrofuran (Fisher Scientific Company) was either freshly distilled from sodium metal and benzophenone or dried for at least 24 hr over activated Linde 4 Å molecular sieves. Boron trifluoride etherate was redistilled prior to use. Fresh bottles of redistilled boron trifluoride etherate purchased from Aldrich Chemical Company, Inc., also usually give good results.

3. Borane-dimethyl sulfide (10 M) was purchased from Aldrich Chemical Company, Inc. and used as received.

4. The potential vigor of this exotherm cannot be overemphasized. It occurs later and is correspondingly stronger if vigorous reflux is not maintained during the addition. The reaction mixture should be watched closely throughout the addition of borane, and addition should be temporarily suspended at the onset of the exotherm.

5. Dimethyl sulfide can be collected if desired by inserting a trap cooled in an acetone-dry ice bath into the hose leading to the bubbler.

6. Yields sometimes drop when an old bottle of borane-dimethyl sulfide is used. Reaction progress can be monitored by thin layer chromatography (silica gel, eluting with 10:10:1 chloroform-methanol-concentrated ammonium hydroxide). Any remaining phenylalanine stains heavily when exposed to ninhydrin ($R_f = 0.35$). If phenylalanine is detected after 5 hr of reflux, an additional 10 mL (0.10 mol) of borane-dimethyl sulfide is added via syringe, and the solution is heated at reflux for 1 additional hr.

7. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1} : 3625, 3360, 3035, 2930, 2855, 1497, 1456, 1032; ^1H NMR (CDCl_3) δ : 1.5-2.0 (broad s, 3 H, NH_2 , OH), 2.5 (dd, 1 H, HCHC_6H_5), 2.8 (dd, 1 H, HCHC_6H_5), 3.1 (m, 1 H, CHNH_2), 3.4 (dd, 1 H, HCHOH), 3.7 (dd, 1 H, HCHOH), 7.1-7.4 (m, 5 H, ArH); $[\alpha]_D -24.7^\circ$ (ethanol, c 1.03). The checkers recorded $[\alpha]_D -22.4^\circ$ (ethanol, c 1.03).

8. Diethyl carbonate (99%) was used as received from Aldrich Chemical Company, Inc.

9. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1} : 3460, 3020, 1760, 1480, 1405, 1220; ^1H NMR (CDCl_3) δ : 2.9 (d, 2 H, $\text{CH}_2\text{C}_6\text{H}_5$), 4.0-4.6 (m, 3 H, CHCH_2O), 5.6 (broad s, 1 H, NH), 7.1-7.5 (m, 5 H, ArH); $[\alpha]_D +4.9^\circ$ (ethanol, c 1.10).

10. The enantiomeric excess was determined to be >99% by capillary GLC analysis (30 m x 32 mm WCOT column coated with Carbowax 20 M, hydrogen carrier gas, linear velocity ca. 94 cm/s, oven temperature 225°C) of the imide derived from the Mosher acid chloride.²

3. Discussion

The utilization of α -amino acids and their derived β -amino alcohols in asymmetric synthesis has been extensive.³ A number of procedures have been reported for the reduction of a variety of amino acid derivatives; however, the direct reduction of α -amino acids with borane has proven to be exceptionally convenient for laboratory-scale reactions.⁴ These reductions characteristically proceed in high yield with no perceptible racemization. The resulting β -amino alcohols can, in turn, be transformed into oxazolidinones, which have proven to be versatile chiral auxiliaries. Besides the highly diastereoselective aldol addition reactions,⁵ enolates of N-acyl oxazolidinones have been used in conjunction with asymmetric alkylations,⁶ halogenations,⁷ hydroxylations,⁸ acylations,⁹ and azide transfer processes,¹⁰ all of which proceed with excellent levels of stereoselectivity.

The phenylalanine-derived oxazolidinone featured here enjoys three practical advantages over the valine-derived oxazolidinone developed earlier in this laboratory.⁵ First, both the intermediate β -amino alcohol and the derived oxazolidinone are crystalline solids which can be purified conveniently by direct crystallization. Second, the oxazolidinone contains a UV chromophore which greatly facilitates TLC or HPLC analysis when it is employed as a chiral auxiliary. Finally, both enantiomers of phenylalanine are readily available, enabling stereocontrol in either sense simply by using the oxazolidinone derived from the appropriate enantiomer.

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Appendix

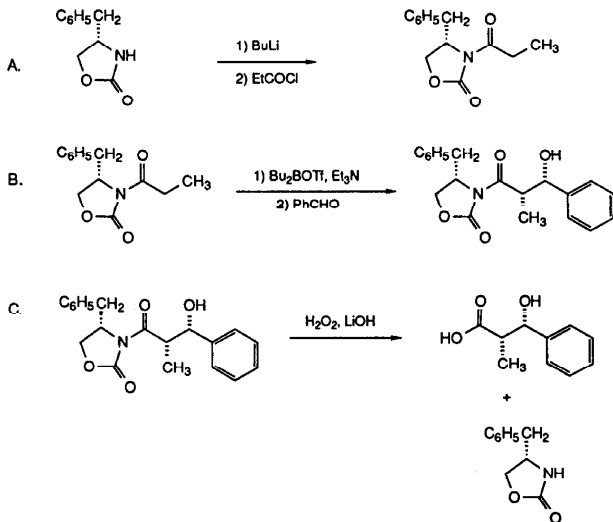
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-4-(Phenylmethyl)-2-oxazolidinone: 2-Oxazolidinone, 4-(phenylmethyl)-,
(S)- (11); (90719-32-7)

(S)-Phenylalanol: 1-Propanol, 2-amino-3-phenyl-, L- or (S)-(-)- (8);
Benzenepropanol, 2-amino-, (S)- (9); (3182-95-4)

(S)-Phenylalanine: Alanine, phenyl-, L- (8); L-Phenylalanine (9); (63-91-2)

**DIASTEREOSELECTIVE ALDOL CONDENSATION
USING A CHIRAL OXAZOLIDINONE AUXILIARY:
(2*S**,3*S**)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID**



Submitted by James R. Gage and David A. Evans.¹

Checked by Donald T. DeRussy and Leo A. Paquette.

1. Procedure

A. (*S*)-3-(1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone. A dry, 500-mL flask equipped with a magnetic stirring bar is charged with 17.7 g (0.100 mol) of (*S*)-4-(phenylmethyl)-2-oxazolidinone,² capped with a rubber septum, and

flushed with nitrogen. Anhydrous tetrahydrofuran, 300 mL (Note 1), is then added to the flask via cannula, and the resulting solution is cooled to -78°C in an acetone-dry ice bath. A solution of 68.3 mL (0.101 mol) of 1.47 M butyllithium in hexane (Note 2) is transferred via cannula first to a dry, septum-stoppered, 100-mL graduated cylinder with a ground glass joint, then to the reaction flask over a 10-min period. The solution may turn yellow and slightly cloudy. Freshly distilled propionyl chloride (9.6 mL, 0.11 mol, Note 3) is added in one portion by syringe after completion of the addition of butyllithium. The resulting clear, nearly colorless solution is stirred for 30 min at -78°C , then allowed to warm to ambient temperature over a 30-min period. Excess propionyl chloride is quenched by the addition of 60 mL of saturated aqueous ammonium chloride. The bulk of the tetrahydrofuran and hexane is removed on a rotary evaporator (bath temp. ca. $25-30^{\circ}\text{C}$), and the resulting slurry is extracted with two 80-mL portions of dichloromethane. The combined organic extracts are washed with 75 mL of an aqueous 1 M sodium hydroxide solution and 75 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed by rotary evaporation, and the residue, a light yellow oil, is placed in a refrigerator overnight to crystallize. The resulting crystalline solid is pulverized and triturated with a minimum quantity of cold hexane. After filtration and drying 21.2-22.3 g (91-96%) of the desired product is obtained as a colorless crystalline solid, mp $44-46^{\circ}\text{C}$ (Notes 4 and 5).

B. The boron aldol reaction. Into a dry, 2-L flask equipped with a large magnetic stirring bar is introduced 21.2 g (0.091 mol) of the acylated oxazolidinone. The flask is sealed with a rubber septum and swept with nitrogen. The solid is dissolved in 200 mL of anhydrous dichloromethane (Note 6), which is introduced via syringe. A thermometer is inserted through the

rubber septum, and the contents of the flask are cooled to 0°C with an ice bath. To this cooled solution is added via syringe 27 mL (0.107 mol) of dibutylboron triflate followed by 16.7 mL (0.120 mol) of triethylamine (Note 7) dropwise at such a rate as to keep the internal temperature below +3°C. The solution may turn slightly yellow or green during the dibutylboron triflate addition, and then to light yellow when triethylamine is added. The ice bath is then replaced with a dry ice-acetone bath (Note 8). When the internal temperature drops below -65°C, 10.3 mL (0.101 mol) of freshly distilled benzaldehyde is added over a 5-min period via syringe. The solution is stirred for 20 min in the dry ice-acetone bath, then for 1 hr at ice bath temperature. The reaction mixture is quenched by the addition of 100 mL of a pH 7 aqueous phosphate buffer and 300 mL of methanol. To this cloudy solution is added by syringe 300 mL of 2:1 methanol-30% aqueous hydrogen peroxide at such a rate as to keep the internal temperature below +10°C. After the solution is stirred for 1 additional hr, the volatile material is removed on a rotary evaporator at a bath temperature of 25-30°C. The resulting slurry is extracted with three 500-mL portions of diethyl ether. The combined organic extracts are washed with 500 mL of 5% aqueous sodium bicarbonate and 500 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, to afford 35-36 g of a white solid (Note 9). The unpurified aldol adduct has a diastereomeric purity of >97% as determined by gas chromatography (Note 10). The solid is recrystallized from ca. 500 mL of 1:2 ethyl acetate-hexane, to yield 25.8 g (84%) of the desired aldol adduct, mp 92-93°C (Note 12). The mother liquor is purified by flash chromatography (column dimensions: 8 cm x 30 cm) with flash-grade silica gel (Note 13).³ Upon elution with 25% ethyl acetate-hexane, an additional 2.8 g (9%) of diastereomerically pure material is obtained.

C. *Chiral auxiliary removal.* A 500-mL flask fitted with a magnetic stirring bar is charged with 8.48 g (0.025 mol) of the aldol adduct and 125 mL of 4:1 tetrahydrofuran-distilled water. The flask is sealed with a rubber septum, purged with nitrogen, and cooled to 0°C in an ice bath. To this solution is added via syringe 10.2 mL (0.100 mol) of 30% aqueous hydrogen peroxide (Note 14) over a 5-min period, followed by 0.96 g (0.040 mol) of lithium hydroxide in 50 mL of distilled water. Some gas evolves from the clear solution. After the solution is stirred for 1 hr, the septum is removed, and 12.6 g (0.100 mol) of sodium sulfite in 75 mL of distilled water is added. The bulk of the tetrahydrofuran is removed on a rotary evaporator at a bath temperature of 25-30°C, and the resulting mixture (pH 12-13) is extracted with three 100-mL portions of dichloromethane to remove the oxazolidinone auxiliary. The aqueous layer is cooled in an ice bath and acidified to pH 1 by the addition of an aqueous 6 M hydrochloric acid solution. The resulting cloudy solution containing the β -hydroxy acid is then extracted with five 100-mL portions of ethyl acetate. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated, affording 5.1 g of a white crystalline solid, which is dissolved in approximately 200 mL of an aqueous 5% sodium bicarbonate solution. This solution is extracted with two 100-mL portions of dichloromethane and then acidified and extracted with ethyl acetate as before. The combined dichloromethane extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford 4.35 g (99%) of the oxazolidinone auxiliary as a white crystalline solid. This solid is recrystallized from 50 mL of 2:1 ethyl acetate-hexane to give 3.95 g (89%) of the recovered oxazolidinone as white crystals, mp 85-87°C. The combined ethyl acetate extracts are dried over anhydrous magnesium sulfate, filtered, and

concentrated to afford 4.50 g (100%) of the desired hydroxy acid as a white crystalline solid, which is recrystallized from ca. 20 mL of carbon tetrachloride to give 4.00-4.03 g (89-90%) of pure (2S*,3S*)-3-hydroxy-3-phenyl-2-methylpropanoic acid, mp 89.5-90°C (Note 15).

2. Notes

1. Reagent grade tetrahydrofuran was purchased from Fisher Scientific Company and either freshly distilled from sodium metal and benzophenone or dried at least 3 days over activated Linde 4 Å molecular sieves before use in reaction A. It was used as received for reaction C.

2. Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc. and titrated prior to use.⁴

3. Propionyl chloride (d, 1.065) was obtained from Aldrich Chemical Company, Inc., and distilled prior to use.

4. Trituration by the checkers gave 21.2-22.3 g (91-96%) of acylated product of somewhat higher purity: mp 45-46°C; $[\alpha]_D^{22} +99.5^\circ$ (ethanol, c 1.01). Alternatively, the acylated oxazolidinone can be isolated by distillation (Kugelrohr, 125°C, 12 mm). Isolated yields are 97-99%.

5. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1} : 3030, 2980, 1780, 1705, 1455, 1385, 1245, 1210, 1080; ^1H NMR (CDCl_3) δ : 1.2 (t, 3 H, $J = 7.2$, CH_3), 2.8 (dd, 1 H, $J = 13.3$, 9.6, $\text{CH}_2\text{C}_6\text{H}_5$), 2.9 (m, 2 H, CH_2CH_3), 3.3 (dd, 1 H, $J = 13.4$, 3.3, $\text{CH}_2\text{C}_6\text{H}_5$), 4.1 (m, 2 H, CHCH_2O), 4.7 (m, 1 H, NCH), 7.1-7.5 (m, 5 H, ArH); $[\alpha]_D^{22} +92.9^\circ$ (ethanol, c 1.01).

6. Dichloromethane was distilled from calcium hydride.

7. Dibutylboron triflate was prepared according to the method of Mukaiyama.⁵ It is also available from Aldrich Chemical Company, Inc. as a solution in dichloromethane or diethyl ether, but results with this material are inconsistent. It should be used within 2 weeks of preparation or after redistillation. Triethylamine (Fisher Scientific Company) was distilled from calcium hydride immediately prior to use.

8. The entire reaction can be carried out at 0°C if desired. The ratio of diastereomers in the unpurified product mixture falls slightly to 97.6:0.2:2.2 (Note 10).

9. The checkers isolated a colorless viscous oil which crystallized upon addition of 1:2 ethyl acetate-hexane. Care must be taken to avoid an excess of hexane, since oiling of the product can occur under these circumstances.

10. Diastereomer ratios were determined by gas chromatography. Since the aldol adduct undergoes retroaldol reaction on the column, it must be silylated prior to injection. Approximately 5 mg of the crude adduct is filtered through a short plug of silica gel to remove any trace metals. The material is taken up into 1-2 mL of dichloromethane in a 2-mL flask or small test tube. To this solution are added 4-5 drops of N,N-diethyl-1,1,1-trimethylsilylamine and a small crystal of 4-(N,N-dimethylamino)pyridine (Note 11). The solution is stirred for 2 hr and injected directly onto the column. (Column conditions: 30 m x 0.32 mm fused silica column coated with DB 5, 14 psi hydrogen carrier gas, oven temperature 235°C).

11. N,N-Diethyl-1,1,1-trimethylsilylamine and 4-(N,N-dimethylamino)-pyridine were purchased from Aldrich Chemical Company, Inc.

12. The product has the following spectroscopic characteristics: IR (solution in dichloromethane) cm^{-1} : 3520, 3040, 2980, 1780, 1695, 1455, 1385, 1210, 1110; ^1H NMR (CDCl_3) δ : 1.2 (d, 3 H, $J = 7.0$, CH_3), 2.8 (dd, 1 H, $J = 13.4$, 9.5, 1 H $\text{CH}_2\text{C}_6\text{H}_5$), 3.1 (d, 1 H, $J = 2.7$, OH), 3.3 (dd, 1 H, $J = 13.4$, 3.4, $\text{CH}_2\text{C}_6\text{H}_5$), 4.1 (m, 3 H, CHCH_2O , CHCH_3), 4.6 (m, 1 H, NCH), 5.1 (m, 1 H, HOCH), 7.1-7.5 (m, 10 H, ArH); $[\alpha]_D^{25} +75.7^\circ$ (dichloromethane, c 1.00).

13. Kieselgel 60 was purchased from EM Science, Cherry Hill, NJ, an affiliate of E. Merck, Darmstadt.

14. Hydrogen peroxide was obtained from Mallinckrodt, Inc.

15. The following spectroscopic characteristics were observed: IR (solution in dichloromethane) cm^{-1} : 3600, 3400-2300 broad hump, 3040, 3000, 1710, 1455, 1230; ^1H NMR (CDCl_3) δ : 1.2 (d, 3 H, $J = 7.1$, CH_3), 2.9 (m, 1 H, CHCH_3), 5.2 (d, 1 H, $J = 3.9$, $\text{C}_6\text{H}_5\text{CH}$), 7.2-7.4 (m, 5 H, ArH); $[\alpha]_D^{22} -26.4^\circ$ (CH_2Cl_2 , c 1.04). No epimerization was detected by NMR.

3. Discussion

This procedure demonstrates a particularly effective method for controlling the relative and absolute stereochemistry of the aldol reaction. It is quite general in scope.⁶ Alkyl-, aryl, and α,β -unsaturated aldehydes all give good results. In addition to chiral propionates,⁷ a range of related aldol reactions may be carried out. For example, the analogous aldol reactions of thioalkyl,⁷ benzyloxy,⁸ or haloacetate,⁹ as well as succinate-⁷ and crotonate-derived¹⁰ carboximides, have been reported.

In addition to the high levels of asymmetric induction, two other attractive features of this sequence of reactions warrant comment. First, both acylation and hydrolysis of the chiral auxiliary are facile, high yield reactions. Second, we have recently found that the lithium hydroperoxide hydrolysis protocol described in Part C is the method of choice for the *deacylation* process. This reagent exhibits remarkable regioselectivity for attack at the desired exocyclic acyl carbonyl moiety.¹¹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-(1-Oxopropyl)-4-(S)-phenylmethyl-2-oxazolidinone: 2-Oxazolidinone,

3-(1-oxopropyl)-4-(phenylmethyl)-, (S)- (11); (101711-78-8)

(S)-4-(Phenylmethyl)-2-oxazolidinone: 2-Oxazolidinone, 4-(phenylmethyl)-.

(S)- (11); (90719-32-7)

Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

Dibutylboron triflate: Methanesulfonic acid, trifluoro-, anhydride with dibutylborinic acid (9); (60669-69-4)

Benzaldehyde (8,9); (100-52-7)

N,N-Diethyl-1,1,1-trimethylsilylamine: Silylamine, N,N-diethyl-1,1,1-trimethyl- (8); Silanamine, N,N-diethyl-1,1,1-trimethyl- (9); (996-50-9)

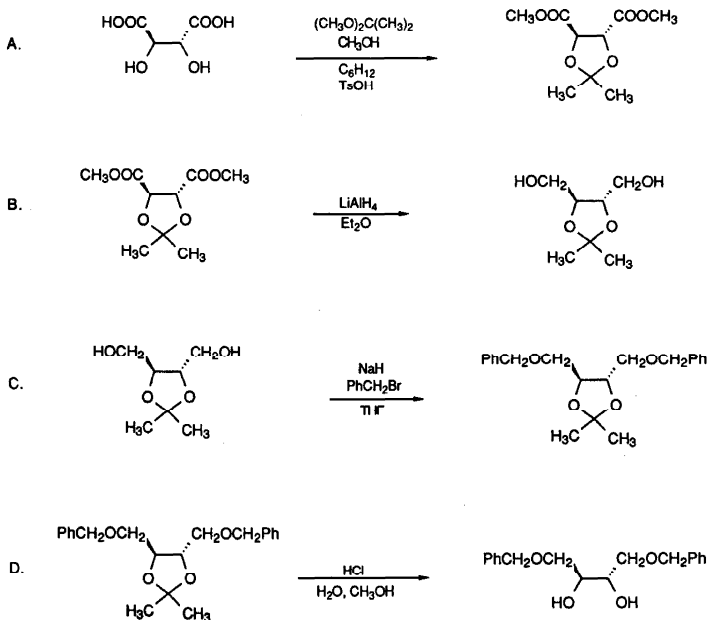
4-(N,N-Dimethylamino)pyridine: Pyridine, 4-(dimethylamino)- (8);

4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

1,4-DI-O-ALKYL THREITOLS FROM TARTARIC ACID:

1,4-DI-O-BENZYL-L-THREITOL

(2,3-Butanediol, 1,4-bis(phenylmethoxy)- [S-(R*,R*)]-)



Submitted by Eugene A. Mash, Keith A. Nelson, Shawne Van Deusen,
and Susan B. Hemperly.¹

Checked by Peter D. Theisen and Clayton H. Heathcock.

1. Procedure

A. *Dimethyl 2,3-O-isopropylidene-L-tartrate* (Note 1). In a 1-L, one-necked, round-bottomed flask fitted with a reflux condenser and a large magnetic stirring bar under argon, a mixture of L-tartaric acid (101 g, 0.673 mol) (Note 2), 2,2-dimethoxypropane (190 mL, 1.61 g, 1.54 mol) (Note 3), methanol (40 mL) (Note 4), and p-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) (Note 5) is warmed on a steam bath with occasional swirling until a dark red homogeneous solution is obtained (Note 6). Additional 2,2-dimethoxypropane (95 mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) (Note 7) are added and the flask is fitted with a 30-cm Vigreux column and a variable reflux distilling head. The mixture is heated to reflux with internal stirring and the acetone-cyclohexane and methanol-cyclohexane azeotropes are slowly removed (Note 8). Additional 2,2-dimethoxypropane (6 mL, 5.1 g, 49 mmol) is then added and the mixture heated under reflux for 15 min (Note 9). After the mixture has cooled to room temperature, anhydrous potassium carbonate (1 g, 7.2 mmol) is added and the mixture is stirred until the reddish color has abated (Note 10). Volatile material is removed under reduced pressure (water aspirator) and the residue is fractionally distilled under vacuum to afford the product as a pale yellow oil, bp 94-101°C (0.5 mm); 125-135 g (0.57-0.62 mmol, 85-92% yield) (Notes 11 and 12).

B. *2,3-Di-O-isopropylidene-L-threitol* (Note 13). In a dry, 2-L, three-necked, round-bottomed flask equipped with a 500-mL pressure-equalized addition funnel, reflux condenser, thermometer, and a large magnetic stirring bar, is suspended lithium aluminum hydride (36 g, 0.95 mol) (Note 14) in diethyl ether (600 mL) (Note 15) under argon. The mixture is stirred and heated to reflux for 30 min. Heating is discontinued while a solution of

dimethyl 2,3-O-isopropylidene-L-tartrate (123 g, 0.564 mol) in diethyl ether (300 mL) (Note 15) is added dropwise over 2 hr. Heating is then resumed and the mixture is refluxed for an additional 3 hr. The mixture is cooled to 0-5°C (Note 16) and *cautiously* treated with water (36 mL), 4 N sodium hydroxide solution (36 mL), and water (112 mL) (Note 17). The mixture is then stirred at room temperature until the grey color of unquenched lithium aluminum hydride has completely disappeared (Note 18). The mixture is filtered on a Büchner funnel and the inorganic precipitate is extracted with ether in a Soxhlet apparatus (Note 19). The combined ethereal extracts are dried over anhydrous magnesium sulfate and filtered, and volatile material is removed under reduced pressure (water aspirator). The residue is fractionally distilled under vacuum to afford the product as a colorless to pale yellow oil, bp 94-106°C (0.4 mm); 50.2-60.3 g (0.31-0.37 mmol, 54-66% yield) (Notes 20 and 21).

C. *1,4-Di-O-benzyl-2,3-di-O-isopropylidene-L-threitol*. In a 2-L, three-necked, round-bottomed flask, equipped with a large magnetic stirring bar under argon, is placed fresh sodium hydride (33.6 g of a 55% dispersion in oil; 18.5 g, 0.77 mol) (Note 22). The oil is removed by washing with hexanes (3 x 100 mL) (Notes 23 and 24). The flask is fitted with a 500-mL pressure-equalized addition funnel, a reflux condenser, and a stopper. Tetrahydrofuran (250 mL) (Note 25) is added under argon. A solution of 2,3-di-O-isopropylidene-L-threitol (55 g, 0.34 mol) in tetrahydrofuran (250 mL) is then added dropwise with stirring at room temperature (Note 26). Benzyl bromide (91 mL, 130.8 g 0.76 mol) (Note 27) is then added dropwise via the addition funnel (Note 28). After stirring for 12 hr at room temperature, the mixture is heated at reflux for 2 hr, cooled in an ice bath, and quenched by addition of water until a clear solution results. Tetrahydrofuran is removed under

reduced pressure (water aspirator); the residue is diluted with water (500 mL) and extracted with diethyl ether (3 x 500 mL). The extracts are combined, dried over anhydrous magnesium sulfate, and filtered. Removal of volatile material under reduced pressure (water aspirator) gives crude 1,4-di-O-benzyl-2,3-O-isopropylidene-L-threitol as an oil (115-116 g).

D. *1,4-Di-O-benzyl-L-threitol*. The crude ketal is dissolved in methanol (300 mL), 0.5 N hydrochloric acid (30 mL) is added, and the resulting mixture is heated to reflux. Acetone and methanol are slowly distilled off (Note 29). Additional methanol (50 mL) and 0.5 N hydrochloric acid (20 mL) are added and the mixture is kept at room temperature until ketal hydrolysis is complete. The mixture is diluted with saturated sodium bicarbonate solution (500 mL) and extracted with ether (3 x 500 mL). The ether extracts are combined, dried over anhydrous magnesium sulfate, and filtered. Removal of volatile material under reduced pressure gives crude 1,4-di-O-benzyl-L-threitol as a pale yellow solid. This solid is recrystallized twice from chloroform/hexanes, to provide 59-65 g (195-215 mmol, 57-63% yield) of pure diol, mp 54-55°C (Notes 30 and 31). Concentration of the mother liquors from the recrystallizations gives a yellow solid which is chromatographed on 70-230 mesh silica gel 60 (500 g) (Note 32), and eluted with 50% ethyl acetate/hexanes, to provide an additional 20-26 g (66-86 mmol, 19-25% yield) of diol, mp 56-57°C (Note 33).

2. Notes

1. Dimethyl 2,3-O-isopropylidene-L-tartrate is also commercially available from Fluka Chemical Corporation.

2. L-Tartaric acid, 99+%, mp 170-172°C, $[\alpha]_D^{20} +12.4^\circ$ (water, d 20), from Aldrich Chemical Company, Inc., was used as obtained.
3. 2,2-Dimethoxypropane, 98%, from Aldrich Chemical Company, Inc., was distilled before use. The checkers used this material directly from the bottle without adverse effects.
4. Methanol was distilled from sodium methoxide before use. The checkers used absolute methanol from Fisher Chemical Company directly from the bottle without adverse effects.
5. p-Toluenesulfonic acid monohydrate, 99%, from Aldrich Chemical Company, Inc., was used as obtained.
6. This normally requires 1-2 hr.
7. Reagent grade cyclohexane, from MCB Manufacturing Chemists Inc., was used as obtained.
8. Removal over a 2-day period (10-15 mL/hr) is satisfactory. After approximately 600 mL of distillate has been collected, the temperature at the solvent head is approximately 79°C.
9. The checkers omitted this final addition and 15-min reflux period without adverse effects.
10. This normally occurs within 1-2 hr, leaving a yellow solution.
11. This product was \geq 88% pure based on recovery of an analytical sample from chromatography on silica gel 60 eluted with 30% ethyl acetate/hexanes. Physical properties and spectral data are as follows: $[\alpha]_D^{24} -42.6^\circ$ (CHCl₃, d 5.1), lit. $[\alpha]_D^{20} -49.4^\circ$ (neat);² IR (neat) cm⁻¹: 2992, 2956, 1759, 1438, 1384, 1213, 1111, 1013, 858, 749; ¹H NMR (CDCl₃) δ : 1.49 (s, 6 H), 3.83 (s, 6 H), 4.81 (s, 2 H); ¹³C NMR (CDCl₃) δ : 25.98, 52.42, 76.68, 113.49, 169.75. The checkers found this material to be 91-94% pure by gas chromatography.

12. Dimethyl 2,3-O-isopropylidene-D-threitol was prepared similarly.
13. 2,3-O-Isopropylidene-L-threitol is also commercially available from Aldrich Chemical Company, Inc. and from Fluka Chemical Corporation.
14. Lithium aluminum hydride, 95+%, from Aldrich Chemical Company, Inc., was used as obtained.
15. Diethyl ether was distilled from sodium immediately prior to use.
16. An ice/salt or ice/acetone bath is employed.
17. Dropwise addition via a funnel is recommended. During the quenching procedure, stirring becomes difficult for a time and manual swirling may be necessary. Use of a stirrer with a powerful magnet is recommended.
18. *Cautious* scraping of the sides of the flask to expose isolated pockets of unquenched lithium aluminum hydride may be expeditious at this point.
19. The checkers obtained a greater yield by carrying out the Soxhlet extraction with tetrahydrofuran instead of ether.
20. This product was $\geq 80\%$ pure based on recovery of an analytical sample from chromatography on silica gel 60 eluted with 80% ethyl acetate/hexanes. Physical properties and spectral data are as follows: $[\alpha]_D^{24} +2.78^\circ$ (CHCl_3 , c 4.67), lit. $[\alpha]_D^{20} +4.1^\circ$ (CHCl_3 , c 5);³ IR (neat) cm^{-1} : 3413, 2987, 2934, 1455, 1372, 1218, 1166, 1057, 986, 882, 844, 801, 756; ^1H NMR (CDCl_3) δ : 1.42 (s, 6 H), 3.73 (m, 6 H), 3.94 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 26.75, 62.06, 78.32, 109.08. The checkers found this material to be 95-97% pure by gas chromatography.
21. 2,3-Di-O-isopropylidene-D-threitol was prepared similarly.
22. Sodium hydride. 55-60% dispersion in mineral oil. from Alfa Products, Morton/Thiokol Inc., was used as obtained.
23. Hexanes were distilled from calcium hydride prior to use.

24. The hexane washes can be decanted into a large beaker containing isopropyl alcohol and dry ice. The last traces of hexanes can be removed under vacuum, followed by reintroduction of an argon atmosphere.

25. Tetrahydrofuran was distilled from sodium immediately prior to use.

26. Toward the end of this addition stirring becomes increasingly difficult. Use of a stirrer with a powerful magnet is recommended.

27. Benzyl bromide from Fluka Chemical Corporation was used as obtained.

28. If magnetic stirring is impossible at this point, manual swirling of the flask may be necessary for a time. As the alkylation proceeds, the mixture becomes less viscous.

29. This requires 3-5 hr. Progress of this hydrolysis can be monitored by thin layer chromatography on 0.25-mm silica gel 60 plates eluted with 50% ethyl acetate/hexanes; R_f ketal 0.59, R_f diol 0.21.

30. Physical properties and spectral data for 1,4-di-O-benzyl-L-threitol are as follows: $[\alpha]_D^{24} -5.85^\circ$ (CHCl_3 , c , 5.15), lit. $[\alpha]_D^{25} -5.0$ (CHCl_3 , c 5);⁴ IR (CHCl_3) cm^{-1} : 3562, 3065, 3014, 2867, 1495, 1453, 1361, 1233, 1101, 1027; ^1H NMR (CDCl_3) δ : 2.93 (br s, 2 H), 3.54-3.60 (m, 4 H), 3.83-3.87 (m, 2 H), 4.47-4.57 (m, 4 H), 7.23-7.36 (m, 10 H); ^{13}C NMR (CDCl_3) δ : 70.45, 71.85, 73.45, 121.70, 128.31, 131.66.

31. 1,4-Di-O-benzyl-D-threitol was prepared similarly; $[\alpha]_D^{24} +6.16^\circ$ (CHCl_3 , c 3.83).

32. E. Merck 70-230 mesh silica gel 60 from Curtin-Matheson Scientific was employed.

33. The checkers found that the solid obtained by recrystallization from chloroform/hexanes occludes a large amount of solvent. To obtain pure, dry material, it is necessary to press the moist solid while it is still on the Büchner funnel and then to dry it under vacuum (room temperature, 0.05 mm, 12-

18 hr). Only 35 g of pure material was obtained in this manner. Repetition of the process with the mother liquors yielded another 35 g of material. The remaining product (ca. 20 g) was obtained by chromatography. Recrystallization from ethyl acetate/hexanes gave a product that is easier to dry.

3. Discussion

Homochiral molecules readily available from inexpensive sources are useful synthetic building blocks and chiral auxiliaries. 1,4-Di-O-benzyl-L-threitol has been used in construction of homochiral crown ethers that are useful as enzyme model systems.⁵ Topologically controlled diastereoselective delivery of the Simmons-Smith reagent for 2-cycloalken-1-one 1,4-di-O-benzyl-L-threitol ketals was recently reported.⁶

A number of other enantioselective processes are known to depend on homochiral acetal or ketal participation.⁷ Diols used in these reactions include tartrate esters, tartramides, propanediols, butanediols, and pentanediols. 1,4-Di-O-benzyl-L-threitol may prove superior to other diols since: (a) it can be produced inexpensively in quantity in either enantiomeric form; (b) it is an amorphous solid; (c) it contains a UV chromophore, making derivatives easy to monitor; (d) it can be introduced directly or via transketalization; (e) it provides "functionalized arms" which can be chemically manipulated after ketalization.

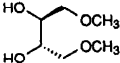
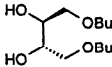
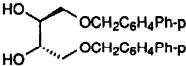
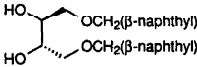
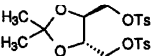
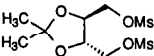
The preparation of 1,4-di-O-benzyl-L-threitol described here from L-tartaric acid via 2,3-O-isopropylidene-L-threitol is adapted from work by Carmack,² Feit,³ and Inouye.⁴ This general route has been employed by the

submitters and by others for the production of a number of synthetically useful L-threitol derivatives (Table). The corresponding D-threitol derivatives are as easily prepared from commercially available D-tartaric acid.

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TABLE

Electrophile	Threitol Derivative	Yield, % ^a	Reference
Methyl iodide		62	8
Butyl iodide		37	8
4-(Chloromethyl)biphenyl		53	9
2-(Bromomethyl)naphthalene		83	9
p-Toluenesulfonyl chloride		82-90	1, 8, 10
Methanesulfonyl chloride		75-82	2, 11

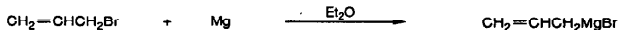
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 1,4-Di-O-benzyl-L-threitol: 2,3-Butanediol, 1,4-bis(benzyloxy)-, (2S,3S)- (8); 2,3-Butanediol, 1,4-bis(phenylmethoxy)-, [S-(R*,R*)]- (9); (17401-06-8)
- Dimethyl 2,3-O-isopropylidene-L-tartrate: 1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester, (4R-trans)- (9); (37031-29-1)
- L-Tartaric acid: Tartaric acid, L- (8); Butanedioic acid, 2,3-dihydroxy-, [R-(R*,R*)]- (9), (87-69-4)
- 2,2-Dimethoxypropane: Propane, 2,2-dimethoxy- (9); (77-76-9)
- 2,3-Di-O-isopropylidene-L-threitol: 1,3-Dioxolane-4,5-dimethanol, 2,2-dimethyl-, (4S-trans)- (9); (50622-09-8)

ALLYLTRIBUTYLTIN

(Stannane, tributyl-2-propenyl-)



Submitted by Noreen G. Halligan and Larry C. Blaszcak.¹

Checked by Christophe M. G. Philippo and Leo A. Paquette.

1. Procedure

Magnesium turnings (72.6 g, 3 g-atom) and 1000 mL of anhydrous ethyl ether are placed under argon in a dry, 3-L, three-necked flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, Claisen adapter, thermometer, ice water-cooled condenser and argon inlet. The dropping funnel is charged with allyl bromide (158 mL, 1.8 mol) (Note 1) in 150 mL of anhydrous ether. Stirring is initiated and a 10-12 mL portion of the allyl bromide solution is run into the reaction flask. The resulting mixture is treated with a few crystals of iodine, whereupon a rise in temperature and clouding of the reaction mixture occurs indicating that the reaction has begun (Note 2). The remainder of the allyl bromide solution is added dropwise with continued stirring at such a rate as to maintain a gentle reflux. The addition requires approximately 1.5 hr. The mixture is then refluxed for an additional 1.5 hr.

While the Grignard solution is being refluxed, the dropping funnel is charged with bis(tributyltin) oxide (371 g, 0.62 mol) (Note 1) in 150 mL of anhydrous ether. After the reflux, heating is stopped and the bis(tributyltin) oxide solution is added at such a rate as to maintain a reaction temperature of 36-38°C. The addition requires approximately 1 hr. After the addition is complete, the reaction mixture is refluxed for 1.5 hr and then stirred overnight at room temperature.

The reaction mixture is cooled in a water-ice bath, and a saturated aqueous ammonium chloride solution is added at such a rate as to maintain the temperature below 35°C. Ammonium chloride solution is added in portions until addition produces no further exothermic reaction (Note 3). The supernatant solution is decanted through glass wool onto 400 g of ice in a 4-L separatory funnel. The residual solids are washed with three portions of hexane, approximately 1000 mL total, and the washes are decanted into the separatory funnel. After the phases are separated, the aqueous phase is washed with an additional 500-mL portion of hexane. The combined organic extracts are washed with 500 mL of saturated ammonium chloride, and then with 500 mL of brine. The organic layer is dried over anhydrous magnesium sulfate and filtered. Most of the solvent is removed by a rotary evaporator and the residual oil is distilled at reduced pressure using an ice water-cooled fraction cutting head. After a small forerun, approximately 390-392 g (94% of theory) is collected as a colorless oil, bp 116°C/1.6 mm (lit. 155°C/17 mm).²

2. Notes

1. Allyl bromide and bis(tributyltin) oxide were obtained from Aldrich Chemical Company, Inc.
2. Initiation of the reaction required about 1 min of sonication in an ordinary laboratory cleaner.
3. Approximately 190 mL of saturated aqueous ammonium chloride is required.

3. Discussion

Within the last decade, organotin chemistry has become a major source of new and highly selective reagents for effecting carbon-carbon bond formation. Transmetallation, nucleophilic substitution, stereoselective carbonyl addition, and transition metal- or radical-mediated substitution reactions have all been accomplished using allyltributyltin. Because of the broad range of selective reactivities under which the synthetically versatile allyl group may be transferred to a highly functionalized substrate, allyltin compounds have secured a position on the modern chemist's list of indispensable reagents.

Transmetallation of allyltributyltin with organolithium species³ has been used for the generation of allyllithium solutions free of the coupling by-products which often result from reduction of allylic halides with lithium metal. These solutions may then be used directly for the preparation of Gilman reagents and other reactive modifications of the parent allyllithium.

The use of allyltributyltin in combination with a Lewis acid has been used to effect both nucleophilic substitution⁴ and stereoselective carbonyl

addition⁵ reactions. These reactions occur with a high degree of selectivity because of the reagent's nucleophilic, completely non-basic character in the presence of a sufficiently reactive carbon electrophile. Allyltin reagents appear to be more useful than the corresponding allylsilanes for these purposes.

By far the most generally useful synthetic application of allyltributyltin is in the complementary set of transition metal- and radical-mediated substitution reactions. When the halide substrates are benzylic, allylic, aromatic or acyl, transition metal catalysis⁶ is usually the method of choice for allyl transfer from tin to carbon. When the halide (or halide equivalent) substrate is aliphatic or alicyclic, radical chain conditions⁷ are appropriate, as β -hydrogen elimination is generally not a problem in these cases.

Allyltriorganotin compounds have been prepared by the reaction of allyl Grignard⁸ or allyllithium reagents with triorganotin halides as well as by the procedure described. This procedure is an adaptation of that used by Rosenberg⁹ for the preparation of vinyltrialkyltin compounds. Allyltriorganotin compounds in which the allyl group bears complex substituents can be prepared by desulfurization of allylic sulfides, sulfoxides, or sulfones with triorganotin hydrides.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

Allyltributyltin: Stannane, allyltributyl- (8); Stannane, tributyl-2-propenyl- (9); (24850-33-7)

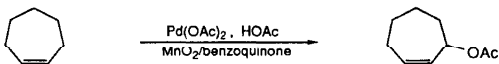
Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

Bis(tributyltin) oxide: Distannoxane, hexabutyl- (8,9); (56-35-9)

ALLYLIC ACETOXYLATION OF CYCLOALKENES:

2-CYCLOHEPTEN-1-YL ACETATE

(2-Cyclohepten-1-ol, acetate)



Submitted by A. Heumann,¹ B. Åkermarck,² S. Hansson,² and T. Rein.²

Checked by Joe Guiles and Albert I. Meyers.

1. Procedure

Palladium acetate (1.12 g, 0.005 mol), benzoquinone (2.16 g, 0.02 mol), manganese dioxide (10.44 g, 0.12 mol) and anhydrous acetic acid (250 mL) (Note 1), are placed in a 1-L, round-bottomed flask equipped with a reflux condenser and magnetic stirring bar. This heterogeneous mixture is equilibrated by efficient stirring for 30-60 min. Cycloheptene (9.61 g, 0.1 mol) (Note 2) is added, and the stirring is continued at 60°C for 28 hr (Note 3). After the solution is cooled to room temperature, 250 mL of pentane/ether (1:1) is added and the mixture is stirred for another 30 min. The two-phase mixture is filtered with suction through a Buchner funnel, which contains a layer of Celite (5-10 mm). The Celite layer is washed successively with 250 mL of pentane/ether (1:1), 250 mL of water, 100 mL of pentane/ether (1:1), and 250 mL of water. After the organic phases are separated, the aqueous phase is extracted three times with 250 mL of pentane/ether (1:1). The combined organic phases are washed successively with 250 mL of water, 250 mL and then

100 mL of aqueous sodium hydroxide (2 N) (Note 4), 250 mL of water, and finally dried over anhydrous magnesium sulfate. After evaporation or distillation of the solvent, the product is purified by distillation (Note 5) to give 2-cyclohepten-1-yl acetate (11.25 g, 73%), bp 61-62°C (5 mm), 11t.³ bp 70°C (6 mm) (Note 6).

2. Notes

1. All the reagents used are analytical grade, commercially available products, which are used without further purification. Darkened benzoquinone was purified by sublimation. Activated grade manganese dioxide was used; however it was not shown that "activation" of manganese dioxide is necessary for the reaction.

2. Reaction conditions for other olefins are shown in Table I.

3. The time for optimized conversion has been determined by GLC for all olefins. It is crucial for all reactions to be stopped at optimum conversion, because slow decomposition of the allylic product occurs during the reaction. To obtain optimum yields one should follow the reaction by GLC. Optimized conversion is defined as: allylic acetate/allylic acetate plus remaining olefin.

4. *Caution should be observed during the alkaline washings because they are exothermic.*

5. The crude reaction products can easily be purified by distillation or by flash chromatography, with hexane/ether (95:5) as eluant.

6. The product exhibits the following NMR spectra: ^1H (200 MHz, CDCl_3) δ : 1.30-2.30 (m, 8 H), 2.05 (s, 3 H), 5.40 (m, 1 H), 5.65 (m, 1 H), 5.82 (m, 1 H); ^{13}C (50.3 MHz, CDCl_3) δ : 21.20, 26.43, 26.48, 28.33, 32.70, 74.13, 131.38, 133.56, 170.24.

3. Discussion

Allylic acetates are usually prepared by esterification from allylic alcohols. However, the corresponding alcohols are often only accessible by the fairly expensive hydride reduction of carbonyl compounds. Consequently, direct allylic functionalization of easily available olefins has been intensively investigated.⁴ Most of these reactions involve peroxides⁵ or a variety of metal salts.^{6,7} However, serious drawbacks of these reactions, (e.g. toxicity of some metals, stoichiometric reaction conditions, or non-generality) may be responsible for their infrequent use for the construction of allylic alcohols or acetates.

Allylic acetoxylation with palladium(II) salts is well known;⁸ however, no selective and catalytic conditions have been described for the transformation of an unsubstituted olefin. In the present system use is made of the ability of palladium acetate to give allylic functionalization (most probably via a palladium- π -allyl complex) and to be easily regenerated by a co-oxidant (the combination of benzoquinone-manganese dioxide). In contrast to copper(II) chloride (CuCl_2) as a reoxidant,⁸ our catalyst combination is completely regioselective for alicyclic alkenes; with aliphatic substrates, evidently, both allylic positions become substituted. As yet, no allylic oxidation reagent is able to distinguish between the two allylic positions in linear olefins; this disadvantage is overcome when the allylic acetates are to

be used as precursors for π -allyl complexes (for example in palladium-catalyzed substitution reactions).

1. Université d'Aix-Marseille, Faculté de St.-Jérôme, UA 126, 13501 F 13397 Marseille Cedex 13, France.
2. Royal Institute of Technology, Department of Organic Chemistry, S 100 44 Stockholm, Sweden.
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TABLE
ALLYLIC ACETOXYLATION OF OLEFINS
















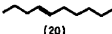
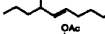




Olefin (mmol)	Pd(OAc) ₂ mmol	MnO ₂ mmol	 mmol	HOAc mL	Temp. °C	Time hr	Yield %	Product ^a	bp °C (mm)	Optimized Conversion (Note 3)
 (100)	5	120	20	250	50	16	66		79-82 (58)	>95 ^b
 (100)	0.5	110	10	250	60	50	77		68 (15)	95
 (100)	5	120	20	250	60	28	73		61-62 (5)	98
 (100)	5	200	20	250	60	90	35 ^c		63-64 (3)	60
 (20)	1	24	4	50	60	300	78		flash (Note 5)	93
 (20)	1	24	4	50	60	43	72 ^d		flash (Note 5)	77
 (2)	0.1	2.4	0.4	5	60	72	>80 ^e		flash (Note 5)	--
 (20)	1	40	4	50	60	68	74		flash (Note 5)	95
 (100)	5	120	20	250	50	30	76		60-62 (3)	98
 (20)	1	40	4	50	40	72	60		flash (Note 5)	85

TABLE (contd.)

^aSome of the products contain small amounts of the homoallylic isomer (5% or less).

^bThe conversion was determined by NMR.

^cThe yield was not corrected; yield based on consumed starting material is 39%.

^dBased on consumed olefin the yield is 90%. The starting olefin was a mixture of approximately 62% trans and 32% cis isomer together with 6% cyclododecane. After the reaction about 20% of the starting material could be recovered, now as a mixture of 20% trans, 50% cis olefin and 30% cyclododecane.

^eThis is a GLC yield using n-decane as internal standard.

^fThe product was a 1:1 mixture.

Appendix

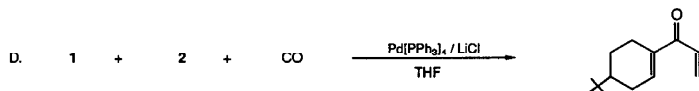
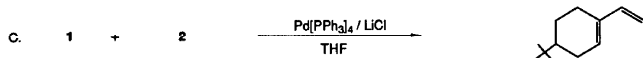
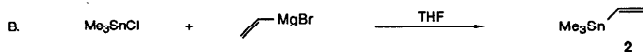
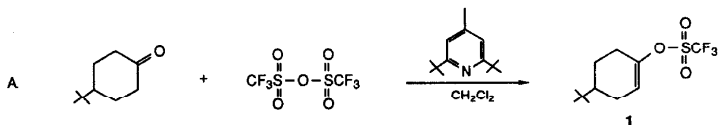
Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

2-Cyclohepten-1-yl acetate: 2-Cyclohepten-1-ol, acetate (8,9); (826-13-1)
Cycloheptene (8,9); (628-92-2)

PALLADIUM-CATALYZED COUPLING OF VINYL TRIFLATES WITH
ORGANOSTANNANES: 4-tert-BUTYL-1-VINYLCYCLOHEXENE AND

1-(4-tert-BUTYLCYCLOHEXEN-1-YL)-2-PROPEN-1-ONE

(Cyclohexene, 4-(1,1-dimethylethyl)-1-ethenyl- and
2-Propen-1-one, 1-[4-(1,1-dimethylethyl)-1-cyclohexen-1-yl])



Submitted by William J. Scott,^{1a} G. T. Crisp,^{1b} and J. K. Stille.^{1c}

Checked by Dean R. Lagerwall and Leo A. Paquette.

1. Procedure

Caution! Many organotin compounds are toxic.² Their preparation and use should be carried out in a well-ventilated hood.

A. *4-tert-Butylcyclohexen-1-yl trifluoromethanesulfonate*. A dry, 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a condenser (Note 1) is charged with 33.0 g (0.214 mol) of 4-*tert*-butylcyclohexanone (Note 2), 1.5 L of dichloromethane (Note 3), and 49.5 g (0.241 mol) of 2,6-di-*tert*-butyl-4-methylpyridine (Note 4). The solution is stirred under a static argon atmosphere and cooled to 0°C, at which time the dropwise addition of 40.0 mL (0.238 mol) of trifluoromethanesulfonic anhydride (Note 5) is begun. After the addition is complete, the brown mixture is allowed to warm slowly to room temperature and is stirred at that temperature for 10 hr. At this point, the consumption of starting ketone is verified by thin layer chromatography (hexane; silica gel). If the reaction is incomplete, more trifluoromethanesulfonic anhydride is added and additional time is allowed. The solvent is removed by distillation and the resulting light tan material is treated with 1 L of pentane and heated to reflux for 30 min. The tan salts thus obtained are removed by filtration and washed with five 100-mL portions of pentane (Note 6). The combined pentane solutions are washed with two 250-mL portions each of a 10% hydrochloric acid solution, a 10% sodium hydroxide solution and a saturated sodium chloride solution, dried with magnesium sulfate, filtered through a 6 x 4-cm pad of silica gel (Note 7), and concentrated by distillation. Bulb-to-bulb distillation (Note 8) of the resulting yellow oil at 75-80°C (0.5 mm) gives 43-45 g (70-73%) of the product as a colorless oil (Note 9).

B. *Trimethylvinyltin*. To a dry, 1-L, three-necked, round-bottomed flask, equipped with a Dewar-type condenser cooled to -78°C, a magnetic stirring bar, and a gas inlet leading to a static supply of dry argon (Note 1), are added 11.4 g (0.469 mol) of clean magnesium turnings, 50 mL of dry tetrahydrofuran (Note 10), 3 mL of vinyl bromide, and 0.3 mL of methyl iodide to initiate

formation of vinylmagnesium bromide. To this is added a solution of 41 mL (0.624 mol or 66.7 g total) of vinyl bromide in 125 mL of dry tetrahydrofuran via cannula at a rate which maintains a gentle reflux. After addition the mixture is heated to reflux for 1 hr with an oil bath, then cooled to 60°C.

To the resulting slurry of vinylmagnesium bromide (with the condenser still maintained at -78°C) is added via cannula a solution of 61.3 g (0.307 mol) of trimethyltin chloride (Note 11) in 50 mL of dry tetrahydrofuran at a rate suitable to maintain a gentle reflux. The temperature is maintained at 60°C for 5 hr and then the mixture is cooled to room temperature. With the condenser still maintained at -78°C, 200 mL of a saturated ammonium chloride solution is added by syringe at a rate which maintains a gentle reflux, followed by 200 mL of water. The resulting solution is transferred to a separatory funnel with the aid of 200 mL of pentane and the organic layer is washed with 250 mL of a saturated ammonium chloride solution. The combined aqueous layers are back-extracted twice with 250 mL of pentane, and the combined organic layers are washed 5 times with 250 mL of saturated ammonium chloride, 10 times with a 10% hydrochloric acid solution, and twice with a saturated sodium chloride solution, then gravity filtered through a 9 x 4-cm pad of silica gel (Note 7) to give approximately 500 mL of a slightly yellow solution. Pentanes are removed by distillation using a 16-cm Vigreux column and a short-path still-head (Note 12). Continued distillation affords a fraction boiling from 60-90°C, which contains a mixture of 4.9 g of trimethylvinyltin in 16.3 g of tetrahydrofuran (Note 13). At this point the still is cooled to room temperature, the Vigreux column is removed, and the remaining oil is distilled at 95-100°C to give 38-39 g (64-66% purified yield) of trimethylvinyltin (Note 14).

C. *4-tert-Butyl-1-vinylcyclohexene*. A dry, 2-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a condenser (Note 1) is charged with 1.18 g (1.02 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 15), 12.9 g (0.305 mol) of lithium chloride (Note 16), and 500 mL of tetrahydrofuran (Note 10). This mixture is stirred for 15 min under a static argon atmosphere; then a solution of 28.0 g (0.0979 mol) of 4-tert-butylcyclohexen-1-yl trifluoromethanesulfonate and 19.0 g (0.0997 mol) of trimethylvinyltin in 250 mL of tetrahydrofuran is added, followed by an additional 250 mL of tetrahydrofuran. The resulting, almost colorless solution is heated to a gentle reflux for 48 hr (Note 17). The mixture is cooled to room temperature and partitioned between 500 mL of water and 250 mL of pentane. The aqueous layer is back-extracted with two 200-mL portions of pentane. The combined organic layers are washed with two 250-mL portions each of a concentrated sodium bicarbonate solution, water, and a concentrated sodium chloride solution, dried over magnesium sulfate, filtered through a 4 x 4-cm pad of silica gel (Note 7) and concentrated by distillation using a 10-cm Vigreux column. Bulb-to-bulb distillation (Note 8) of the resulting yellow oil at 65-68°C (0.55 mm) gives 12.6-12.8 g (78-79%) of the coupled product (Note 18).

D. *1-(4-tert-Butylcyclohexen-1-yl)-2-propen-1-one*. To a dry, 2-L, round-bottomed flask, equipped with a magnetic stirring bar, condenser, and gas inlet connected to a static argon atmosphere (Note 1), are added 1.12 g (0.968 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 15), 13.2 g (0.312 mol) of lithium chloride (Note 16) and 500 mL of tetrahydrofuran (Note 10), followed by a solution of 28.6 g (0.100 mol) of 4-tert-butylcyclohexen-1-yl trifluoromethanesulfonate and 19.1 g (0.100 mol) of trimethylvinyltin in 250 mL of tetrahydrofuran, and then an additional 250 mL of tetrahydrofuran. A gas

bag (Note 19) filled with carbon monoxide is attached to the gas inlet and the apparatus is flushed with carbon monoxide. The gas bag is refilled with carbon monoxide and reattached to the gas inlet. The mixture is then heated to 55°C (Note 20). After 2-4 hr, a large amount of the carbon monoxide has been absorbed into solution and the gas bag is refilled and re-attached to the gas inlet. After a total of 40 hr, the reaction mixture darkens and is cooled to room temperature (Note 21). This solution is transferred to a 2-L separatory funnel, diluted with 500 mL of pentane, and washed with two 200-mL portions each of water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. The resulting yellow solution is dried over magnesium sulfate, filtered through a 6 x 4-cm pad of silica gel (Note 7), and concentrated using a rotary evaporator. Slow bulb-to-bulb distillation (Notes 8 and 22) of the brown oil at 85-95°C (0.35 mm) gives 14.3-14.5 g (74-75%) of the product as a colorless oil (Note 23).

2. Notes

1. The glassware is dried in an oven at 140°C overnight and assembled warm under a static argon atmosphere.
2. 4-tert-Butylcyclohexanone is purchased from the Aldrich Chemical Company, Inc.
3. Dichloromethane is freshly distilled from calcium hydride.
4. 2,6-Di-tert-butyl-4-methylpyridine can be purchased from the Aldrich Chemical Company, Inc. or prepared from pivaloyl chloride.³
5. Trifluoromethanesulfonic anhydride can be purchased from the Aldrich Chemical Company, Inc. or prepared from trifluoromethanesulfonic acid.⁴

6. The solids can range in color from off-white to brown. 2,6-Di-tert-butyl-4-methylpyridine can be recovered by separation of the tan solids between 500 mL of pentane and 650 mL of a 1.2 N sodium hydroxide solution. The aqueous layer is extracted with two 200-mL portions of pentane. The combined organic phases are washed with two 200-mL portions of water and two 200-mL portions of a saturated sodium chloride solution dried with sodium sulfate, filtered through a 6 x 4-cm pad of silica gel (Note 7), and concentrated using a rotary evaporator. Bulb-to-bulb distillation (Note 8) of the yellow oil at 65-75°C (0.55 mm) with trapping of the distillate in two connected receiving flasks cooled to -78°C gives 42.1-48.1 g (85-97%) of colorless oil, which solidifies on standing.

7. Woelm 230-400 mesh silica gel is used.

8. An Aldrich Chemical Company, Inc. Kugelrohr apparatus is used.

9. 4-tert-Butylcyclohexen-1-yl trifluoromethanesulfonate has the following properties: mp 17°C; TLC R_f (hexanes): 0.65; IR (neat) cm^{-1} : 1698, 1440, 1425, 1250, 1225; ^1H NMR (CDCl_3 , 270 MHz) δ : 0.89 (s, 9 H), 1.26-1.38 (m, 3 H), 1.90-2.18 (m, 2 H), 2.23-2.39 (m, 2 H), 5.73-5.75 (m, 1 H); ^{13}C NMR (CDCl_3 , 68 MHz) δ : 23.9, 25.4, 27.2 (3C), 28.6, 32.0, 43.1, 118.3, 118.7 (q, $J = 319$, CF_3), 149.3.

10. Tetrahydrofuran is freshly doubly-distilled from potassium.

11. Trimethyltin chloride can be purchased from Strem Chemicals, Inc. or prepared by the reaction of tetramethyltin with tin tetrachloride as follows: To a 100-mL, round-bottomed flask, equipped with a magnetic stirring bar, and a septum, and a gas inlet connected to a static argon atmosphere, containing 41.2 g (0.230 mol) of tetramethyltin cooled to -20°C with a dry ice/carbon tetrachloride slurry, is added 9.0 mL (0.0769 mol) of tin tetrachloride at a slow dropwise rate. After the addition is complete, the

mixture is heated to 60°C for 16 hr. The mixture is cooled to room temperature to afford 61.3 g (100% yield) of a colorless solid.

12. In order to maximize the yield of trimethylvinyltin, pentanes should be removed as carefully as possible. The authors employed only 14/20-ground glassware in the distillation and carefully controlled the oil bath temperature to maintain a collection rate of approximately 0.3 mL per min.

13. The ratio of trimethylvinyltin to tetrahydrofuran is determined by NMR. The trimethylvinyltin/THF solution may be used in palladium-catalyzed coupling reactions without further purification.

14. Trimethylvinyltin is >97% pure as shown by gas chromatography on a 1/8" x 6' column packed with 6% SP-2100 on Supelcoport, 80-100 mesh, operated at 50°C. The relative retention times are: 1.9 min for tetrahydrofuran, 4.0 min for trimethylvinyltin, and 7.0 min for trimethyltin chloride (not seen). The distilled product has the following properties: ^1H NMR (CDCl_3 , 270 MHz) δ : 0.12 (s, 9 H), 5.66 (dd, 1 H, $J = 3.4, 20.5$), 6.11 (dd, 1 H, $J = 3.6, 13.9$), 6.52 (dd, 1 H, $J = 13.9, 20.5$); ^{13}C NMR (CDCl_3 , 68 MHz) δ : -9.9 (3C) 133.2, 140.0.

15. Tetrakis(triphenylphosphine)palladium(0) can be purchased from Strem Chemicals, Inc. or prepared from palladium chloride.⁵ On standing for a period of time (> a few weeks) the catalyst gradually darkens, turning tan in the absence of oxygen or turning green in the presence of oxygen. However, the coupling reactions run equally well with catalyst that has aged for a year.

16. Lithium chloride is dried at 140°C for 24 hr prior to use.

17. The progress of the reaction is conveniently monitored by gas chromatography using a 1/8" x 6' column packed with 6% SP-2100 on Supelcoport, 80-100 mesh, operated at 50°C for 4 min, then heated at 15°C/min to 250°C.

The relative retention times are: 4.0 min for trimethylvinyltin, 6.5 min for trimethyltin chloride, 12.0 min for 4-tert-butyl-1-vinylcyclohexene, and 13.1 min for 4-tert-butylcyclohexen-1-yl trifluoromethanesulfonate. Because of the extreme volatility of trimethylvinyltin, it may be necessary to add additional small amounts in order to drive the reaction to completion.

18. 4-tert-Butyl-1-vinylcyclohexene has the following properties: bp 45°C (0.1 mm); TLC R_f (hexanes): 0.74; IR (neat) cm^{-1} : 3100, 3020, 1650, 1610, 1395, 1365, 985, 890; ^1H NMR (CDCl_3 , 270 MHz) δ : 0.87 (s, 9 H), 1.08-1.34 (m, 3 H), 1.84-2.36 (m, 4 H), 4.88 (d, 1 H, $J = 10.7$) 5.04 (d, 1 H, $J = 17.5$), 5.73-5.75 (m, 1 H), 6.35 (dd, 1 H, $J = 10.7, 17.5$); ^{13}C NMR (CDCl_3 , 68 MHz) δ : 23.8, 25.3, 27.2 (3C), 27.4, 32.2, 44.4, 109.7, 129.8, 136.0, 139.7.

19. The gas bag can be purchased from the Fisher Scientific Company and is filled to approximately 5 psig with carbon monoxide.

20. Refluxing conditions must be avoided in order to maximize the amount of carbon monoxide in solution.

21. The progress of the reaction is conveniently monitored by gas chromatography on a 1/8" x 6' column packed with 6% SP-2100 on Supelcoport, 80-100 mesh, operated at 50°C for 4 min, then heated at 15°C/min to 250°C. The relative retention times are: 4.0 min for trimethylvinyltin, 6.5 min for trimethyltin chloride, 13.1 min for 4-tert-butylcyclohexen-1-yl trifluoromethanesulfonate, and 14.7 min for 1-(4-tert-butylcyclohexen-1-yl)-2-propen-1-one. Because of the extreme volatility of trimethylvinyltin, it may be necessary to add additional small amounts of this reagent in order to drive the reaction to completion.

22. The purification procedure occasionally leads to product contaminated with organotins. The submitters have found that careful washing with water minimizes this problem. The checkers found that distillation of product at a slow rate allows the unwanted tin to escape to the cold trap.

23. 1-(4-tert-Butylcyclohexen-1-yl)-2-propen-1-one has the following properties: bp 75°C (0.1 mm); IR (neat) cm^{-1} : 1665, 1645, 1612; ^1H NMR (CDCl_3 , 270 MHz) δ : 0.81 (s, 9 H), 1.21-2.65 (m, 7 H), 5.58 (d, 1 H, $J = 9.0$), 6.14 (d, 1 H, $J = 17.2$), 6.75-7.00 (m, 2 H); ^{13}C NMR (CDCl_3 , 68 MHz) δ : 23.3, 24.6, 26.9 (3C), 27.8, 32.0, 43.4, 127.1, 131.5, 139.4, 141.1, 190.8.

3. Discussion

The conversion of a ketone into a substituted olefin is classically achieved by the addition of a Grignard reagent to a ketone, followed by the dehydration of the resulting alcohol. Such a scheme can often lead to a mixture of regioisomers. By converting the ketone into a vinyl iodide,⁶ followed by a cuprate coupling reaction,⁷ it is possible to form selectively the less-hindered, substituted olefin. Group 10⁸-catalyzed coupling reactions of vinyl iodides also lead to the formation of olefins in good yields.⁹⁻¹¹ However, the synthesis of the more hindered vinyl iodides can be quite difficult.

A number of enolate derivatives have recently been offered as alternatives to vinyl iodides. The advantage to such a scheme lies in the ability to form regioselectively either the kinetic or the thermodynamic enolate using known methodology,¹² and then to trap that enolate to give the required derivative. In general, enolate derivatives, such as methyl vinyl ethers,¹³ silyl enol ethers,¹⁴ and enol phosphates,¹⁵ have undergone coupling only in the presence of nickel catalysts, thus requiring the use of very strong nucleophiles. However, such nucleophiles severely restrict the functionality which may be present in either the enolate derivative or the nucleophile.

Vinyl trifluoromethanesulfonates¹⁶ have provided a solution to this problem. Vinyl trifluoromethanesulfonates can be formed by the action of trifluoromethanesulfonic anhydride with a ketone.^{4,16} Enolates may be trapped using N-phenyltrifluoromethanesulfonimide to form selectively either the kinetic or thermodynamic derivative.¹⁷⁻¹⁹ The resulting enolate derivatives couple readily with organocuprates.²⁰ Palladium-catalyzed coupling reactions may also be run to give directly coupled products,¹⁹ Heck-type coupled products,²¹⁻²³ or reduced products.¹⁹⁻²⁴ Direct coupling reactions of vinyl trifluoromethanesulfonates have been used in the synthesis of pleraplysillin-1,¹⁹ the synthesis of cardenolides,²² the synthesis of vinylstannanes,²⁵⁻²⁷ and in intramolecular cyclization reactions.²⁸⁻³⁰

The synthesis of ketones is very important to the organic chemist. Two common methods involve the addition of Grignard reagents to aldehydes, followed by oxidation of the secondary alcohol, and the addition of organolithium reagents to carboxylic acids.³¹ In addition, acid chlorides have been coupled with Grignard reagents,^{32,33} organoaluminum reagents,³⁴ organocadmium reagents,³³ organocuprates,⁷ or organozinc reagents³³ to give the corresponding ketone. More recently, the palladium-catalyzed coupling of acid chlorides with organozinc reagents,³⁵ organostannanes,³⁶ or organomercury reagents³⁷ has provided a very mild method for ketone synthesis.

In order to avoid the necessity of using acid chlorides in the coupling reactions, the palladium-catalyzed coupling of electrophiles in the presence of carbon monoxide was developed.^{38,39} Again, the necessity of using vinyl iodides limits this methodology. Upon palladium-catalyzed coupling of vinyl trifluoromethanesulfonates in the presence of lithium chloride, the desired enones are formed in good yield.^{40,41} The carbonylative coupling reaction has been used in the synthesis of (\pm)- $\Delta^9,12$ -cannabinene.⁴⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number)

(Registry Number)

- 4-tert-Butyl-1-vinylcyclohexene: Cyclohexene, 4-tert-butyl-1-vinyl- (8);
 Cyclohexene, 4-(1,1-dimethylethyl)-1-ethenyl- (9); (33800-81-6)
- 1-(4-tert-Butylcyclohexen-1-yl)-2-propen-1-one: 2-Propen-1-one, 1-[4-(1,1-dimethylethyl)-1-cyclohexen-1-yl]- (11); (92622-56-5)
- 4-tert-Butylcyclohexen-1-yl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, 4-(1,1-dimethylethyl)-1-cyclohexen-1-yl ester (10); (77412-96-5)

4-tert-Butylcyclohexanone: Cyclohexanone, 4-tert-butyl- (8); Cyclohexanone, 4-(1,1-dimethylethyl)- (9); (98-53-3)

2,6-Di-tert-butyl-4-methylpyridine: Pyridine, 2,6-bis(1,1-dimethylethyl)-4-methyl- (9); (38222-83-2)

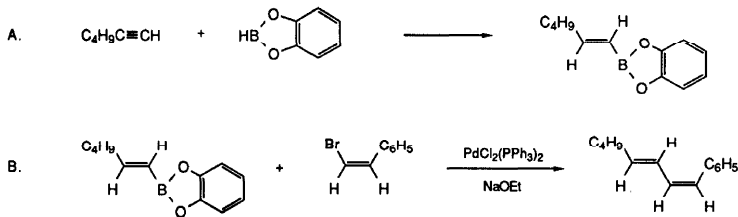
Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

Trimethylvinyltin: Stannane, trimethylvinyl- (8); Stannane, ethenyltrimethyl- (9); (754-06-3)

Trimethyltin chloride: Stannane, chlorotrimethyl- (8,9); (1066-45-1)

Tetrakis(triphenylphosphine)palladium(0): Palladium, tetrakis(triphenylphosphine)- (8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

**PALLADIUM-CATALYZED REACTION OF 1-ALKENYLBORONATES
WITH VINYLIC HALIDES: (1Z,3E)-1-PHENYL-1,3-OCTADIENE
(Benzene, 1,3-octadienyl-, (Z,E)-)**



Submitted by Norio Miyaura and Akira Suzuki.¹

Checked by Albert L. Casalnuovo, Thomas S. Kline, Jr., and Bruce E. Smart.

1. Procedure

A. *(E)*-1-Hexenyl-1,3,2-benzodioxaborole. A 25-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, rubber septum, 10-mL addition funnel, and a reflux condenser. The apparatus is connected through the condenser to a nitrogen source and an oil bubbler (Note 1). The flask is charged with 4.9 g (60 mmol) of 1-hexyne (Note 2) through the addition funnel. While the solution is stirred slowly, 6.7 mL (60 mmol) of catecholborane (Note 3) is injected by syringe through the septum cap. The exothermic reaction is maintained at 60-70°C by intermittent cooling in an ice-water bath. The reaction mixture is allowed to cool to room temperature and is stirred for 15 min. The rubber septum is replaced by a glass stopper,

and the mixture is heated to 60°C and stirred for an additional 2 hr. The flask is cooled to room temperature, the condenser is replaced by a short-path distillation head, and the mixture is distilled at reduced pressure to give 9.5-10.5 g (78-87%) of clear, colorless product, bp 75-76°C (0.10 mm) [lit.² bp 82°C (0.25 mm)] (Note 4).

B. *(1Z,3E)-1-Phenyl-1,3-octadiene*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser to which a nitrogen inlet tube and oil bubbler are attached, a glass stopper, and an addition funnel is flushed with nitrogen and charged with 9.5 g (47 mmol) of (E)-1-hexenyl-1,3,2-benzodioxaborole and 200 mL of benzene (Note 5). The solution is stirred and 8.4 g (46 mmol) of (Z)- β -bromostyrene (Note 6), 50 mL of 2 M sodium ethoxide in ethanol (Note 7), and finally 0.28 g (0.4 mmol) of dichlorobis(triphenylphosphine)palladium(II) (Note 8) are added. The mixture is refluxed for 3 hr. The light brown solution containing a white precipitate of sodium bromide is cooled to room temperature, treated with 60 mL of 3 M sodium hydroxide and 6 mL of 30% hydrogen peroxide, and stirred at room temperature for 1 hr (Note 9). The organic layer is separated, washed four times with 50 mL of 3 M sodium hydroxide (Note 10), and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residual oil is distilled under reduced pressure (Note 11) to give 7.0 g (82%) of (1Z,3E)-1-phenyl-1,3-octadiene as a clear, colorless liquid, bp 80°C (0.15 mm) (Note 12).

2. Notes

1. All glassware was pre-dried in an oven at 130°C for 3 hr, assembled while hot, and allowed to cool under a stream of nitrogen.

2. The preparation of 1-hexyne is described in *Org. Synth., Collect Vol. IV 1963*, 117. The checkers obtained 1-hexyne from Aldrich Chemical Company, Inc., and distilled it prior to use.

3. Catecholborane (1,3,2-benzodioxaborole) with a purity of 95% was purchased from Aldrich Chemical Company, Inc. and purified by distillation under nitrogen, bp 58°C (52 mm). For the distillation and handling of air and moisture sensitive compounds, see references 3-5. Catecholborane is a liquid at room temperature, and the neat material is 9.0 M in catecholborane.³ The preparation of catecholborane from borane and catechol has been reported.³

4. The submitters report bp 86-87°C (0.3 mm). (E)-1-Hexenyl-1,3,2-benzodioxaborole is quite air stable, but it can slowly hydrolyze to boronic acid and turn brown on repeated use in air. The submitters recommend storing it at refrigerator temperature in a bottle purged with nitrogen and capped with a rubber septum. Alternatively, the crude 1-hexenyl-1,3,2-benzodioxaborole can be used for the next coupling reaction without purification. In this case, the unreacted 1-hexyne should be removed under reduced pressure (0.1 mm for 30 min), because it also reacts with (Z)- β -bromostyrene to afford (1Z)-1-phenyl-1-octen-3-yne. In this manner the expected diene was obtained in a yield of 86%.

5. Benzene was obtained from Fisher Scientific Company and redistilled before use.

6. (Z)- β -Bromostyrene was prepared by the procedure described in *Org. Synth. 1984*, 62, 39.

7. The sodium ethoxide solution was prepared by dissolving 2.3 g of sodium in 50 mL of anhydrous ethanol and was used immediately.

8. The palladium catalyst is prepared as follows. A 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux

condenser connected to a nitrogen inlet is flushed with nitrogen and charged with 1.00 g (5.64 mmol) of palladium chloride (Johnson Matthey, Inc.), 3.25 g (12.4 mmol) of triphenylphosphine (Aldrich Chemical Company, Inc.), and 30 mL of benzonitrile (Aldrich Chemical Company, Inc.). The mixture is stirred, gradually heated to 180°C, and held at that temperature for 20 min. The clear, red solution that results is allowed to cool slowly to room temperature and stand overnight. The bright yellow crystals which precipitate are collected by filtration, washed with three 10-mL portions of ether, and dried at reduced pressure to give 3.90 g (5.55 mmol) of dichlorobis(triphenylphosphine)palladium(II).

9. This operation removes most of the palladium-containing compounds. Any unreacted 1-hexenylboronate is oxidized to hexenal.

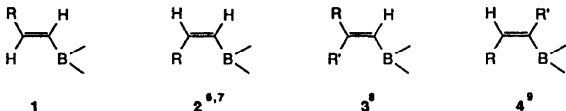
10. Catechol must be washed out completely because it is difficult to remove by distillation. A solution of catechol in aqueous sodium hydroxide turns dark brown on treatment with hydrogen peroxide or on standing in air.

11. The residual oil can be purified before distillation by filtering it through a short (20 cm) silica gel column (70-230 mesh) using hexanes as an eluent. This effectively removes traces of catechol and palladium-containing compounds.

12. Gas chromatographic analysis of the product (Hewlett-Packard fused silica, cross-linked methylsilicone capillary column, 25 m x 20 mm, column temperature 100-270°C, injection temperature 250°C) shows that the product is over 99% chemically and isomerically pure. (Z,E)-1-Phenyl-1,3-octadiene shows the following spectral properties: IR (neat) cm^{-1} : 1640, 1595, 1490, 985; ^1H NMR (CDCl_3) δ : 0.89 (t, 3 H, $J = 7.1$), 1.25-1.45 (m, 4 H), 2.05-2.20 (m, 2 H), 5.87 (d of t, 1 H, $J = 7.1$, 15, $\text{PhC}=\text{C}=\text{CH}$), 6.21 (d of d, 1 H, $J = 11.2$, 11.6, $\text{PhC}=\text{CH}$), 6.30 (d, 1 H, $J = 11.6$, $\text{PhCH}=\text{C}$), 6.60 (d of d, 1 H, $J = 11.2$, 15, $\text{PhC}=\text{C}-\text{CH}=\text{C}$), and 7.15-7.40 (m 5 H, aromatic).

3. Discussion

The procedure described here is an example of a general method for preparing conjugated alkadienes by the palladium-catalyzed reaction of 1-alkenylboranes or boronates with vinylic halides. Hydroboration of 1-alkynes with catechoiborane is a standard method for obtaining (E)-1-alkenylboronates (1).^{2,3} Several different types of alkenylboranes and boronates (2-4) are now available as reagents for the cross-coupling reaction with vinyl halides.



These alkenylboron derivatives react not only with 1-alkenyl halides but also with a variety of other organic halides, including 1-bromo-1-alkynes,⁶ aryl halides,^{7,9,10} and allylic or benzylic halides,¹¹ in the presence of a palladium catalyst and base. Both $\text{Pd}(\text{PPh}_3)_4$ and $\text{PdCl}_2(\text{PPh}_3)_2$ are excellent catalysts for most of the reactions. A base is generally required for successful coupling. Sodium ethoxide (2 equiv) in ethanol-benzene, which is used in the procedure described here, gives high yields with most 1-bromo-1-alkenes. For 1-iodo-1-alkenes, aqueous sodium hydroxide in tetrahydrofuran¹² or aqueous 4 M potassium hydroxide (3 equiv) in benzene⁹ can give better results. Alkoxides and hydroxides normally accelerate the reaction, but the choice of base depends upon its compatibility with the particular organic halide. For the coupling reaction with 3-halo-2-cyclohexen-1-one¹³ a relatively weak base, such as sodium acetate in methanol, works well. The reaction with 1-bromo-2-phenylthio-1-alkenes¹⁴ is successfully carried out using aqueous potassium hydroxide. For the reaction of (E)-2-

ethoxyvinylborane with aryl halides,¹⁵ a suspension of sodium hydroxide in tetrahydrofuran gives better results than homogeneous base. The versatility of these methods has been reviewed.^{8,16}

In addition to alkenylboron compounds, alkenylalane,¹⁷ alkenylzirconium,¹⁸ alkenyltin,¹⁹ alkenylcopper,²⁰ and alkenylmagnesium²¹ reagents are reported to undergo a related alkenyl-alkenyl coupling reaction to give 1,3-alkadienes.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1Z,3E)-1-Phenyl-1,3-octadiene: Benzene, 1,3-octadienyl-, (Z,E)- (9);
(39491-66-2)

(E)-1-Hexenyl-1,3,2-benzodioxaborole: 1,3,2-Benzodioxaborole, 2-(1-hexenyl)-,
(E)- (9); (37490-22-5)

1-Hexyne (8,9); (693-02-7)

Catecholborane: 1,3,2-Benzodioxaborole (8,9); (274-07-7)

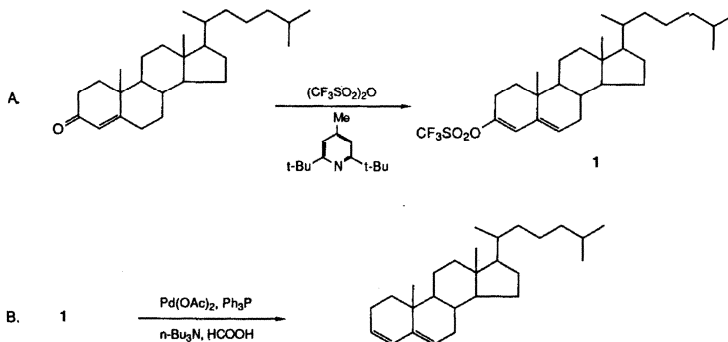
(Z)- β -Bromostyrene: Styrene, β -bromo-, (Z)- (8); Benzene,
(Z-bromoethenyl)- (Z)- (9); 588-73-8)

Dichlorobis(triphenylphosphine)palladium(II): Palladium,
dichlorobis(triphenylphosphine)- (8,9); (13965-03-2)

Palladium chloride (8,9); (7647-10-1)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

**PALLADIUM-CATALYZED REDUCTION OF VINYL TRIFLUOROMETHANESULFONATES
TO ALKENES: CHOLESTA-3,5-DIENE**



Submitted by Sandro Cacchi,¹ Enrico Morera,² and Giorgio Ortar.²

Checked by Sean Kerwin, Christopher Schmid, and Clayton H. Heathcock.

1. Procedure

A. *Cholesta-3,5-dien-3-yl trifluoromethanesulfonate*. A dry, 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, rubber septum, and pressure-equalizing 100-mL dropping funnel fitted with a calcium chloride drying tube is charged with 4.62 g (22.5 mmol) of 2,6-di-tert-butyl-4-methylpyridine (Note 1) and 60 mL of dry dichloromethane (Note 2). Then 3.08 mL (18.75 mmol) of trifluoromethanesulfonic anhydride (Note 3) is added rapidly from a syringe and 5.77 g (15 mmol) of cholest-4-en-3-one (Note 4) diluted in 40 mL of dry dichloromethane is added through the dropping

funnel, dropwise and with stirring, during 15-20 min. The mixture is stirred for an additional 1 hr at room temperature. During this period the solution turns slightly pink and a white precipitate separates. The solvent is removed with a rotary evaporator and the residue is combined with 100 mL of diethyl ether. The white pyridinium trifluoromethanesulfonate salt is filtered off and washed with additional diethyl ether (3 x 50 mL). The ethereal solution is washed with cold 2 N hydrochloric acid (2 x 100 mL) and with saturated sodium chloride solution (3 x 100 mL), dried over anhydrous potassium carbonate, and concentrated at reduced pressure. The solid residue (7.21-7.40 g) is recrystallized from hexane to give 6.46-6.72 g (83-87%) of cholesta-3,5-dien-3-yl trifluoromethanesulfonate as white crystals (Note 5), mp 125-126°C (Note 6).

B. Cholesta-3,5-diene. A 50-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser with a nitrogen inlet at the top is charged with 5.00 g (9.68 mmol) of cholesta-3,5-dien-3-yl trifluoromethanesulfonate (1), 6.92 mL (29.03 mmol) of tributylamine (Note 7), 0.043 g (0.19 mmol) of palladium acetate, 0.100 g (0.38 mmol) of triphenylphosphine, and 20.2 mL of N,N-dimethylformamide. The mixture is gently flushed with nitrogen for 1-2 min and capped with a rubber septum. Formic acid, 99%, 0.73 mL (19.42 mmol) is added from a syringe dropwise and with swirling during 2-3 min. The resulting mixture is warmed in an oil bath at 60°C for 1 hr with continuous stirring under nitrogen. During this period the mixture becomes black. The contents of the flask are poured into 50 mL of 2 N hydrochloric acid and extracted with two 75-mL portions of ethyl ether. The combined organic phases are then washed with 50 mL of 2 N hydrochloric acid, 15 mL of saturated sodium bicarbonate solution, two 10-mL portions of saturated sodium chloride solution, and dried over anhydrous magnesium

sulfate. The drying agent is removed by filtration, the ether is evaporated at reduced pressure, and the solid residue (3.92-4.16 g) is purified by open-column chromatography on 100 g of basic aluminum oxide (Note 8) using hexane as eluent to give 3.12-3.22 g of nearly pure cholesta-3,5-diene which is recrystallized from acetone to give a first crop (2.92-3.00 g) as white needles (Note 9), mp 81.5-82.5°C [lit.³ mp 79.5-80°C] (Note 6) and a second crop (0.11-0.15 g, 85-88% overall yield), mp 79.5-80.5°C (Note 6).

2. Notes

1. A commercial sample of 2,6-di-tert-butyl-4-methylpyridine from Fluka AG was purified through a short column of silica gel by eluting with hexane. Alternatively it may be prepared according to the procedure reported in Organic Syntheses.⁴

2. Reagent grade dichloromethane is dried by passing over a column of aluminum oxide (activity I).

3. Trifluoromethanesulfonic anhydride from Fluka AG was stirred over phosphorus pentoxide for 18 hr and distilled. It can also be prepared from trifluoromethanesulfonic acid (Fluka AG) according to the procedure described in Organic Syntheses.⁵

4. Cholest-4-en-3-one was purchased from Fluka AG and used without further purification.

5. Spectral data are as follows: ¹H NMR (90 MHz, CDCl₃) δ: 0.69 (s, 3 H, 13-CH₃), 0.82 (s, 3 H, 10-CH₃), 5.62 (m, 1 H, C-6 H), 6.02 (m, 1 H, C-4 H); MS m/e: 516 (M⁺).

6. Melting points are uncorrected and were determined with a Köfler hot-stage apparatus.

7. Tributylamine, palladium acetate, triphenylphosphine from Fluka AG and N,N-dimethylformamide and formic acid from Farmitalia Carlo Erba Chemicals were used without further purification.

8. Basic aluminum oxide (activity I) is available from Merck & Company, Inc.

9. This compound has the following physical properties: ^1H NMR (90 MHz, CDCl_3) δ : 0.69 (s, 3 H, 13- CH_3), 0.82 (s, 3 H, 10- CH_3), 5.4 (m, 1 H, C-6 H), 5.59 (m, 1 H, C-3 H), 5.71 (d, 1 H, J = 10, C-4 H); $[\alpha]_D$ (CHCl_3 , 1%) -115° (lit.³ $[\alpha]_D -123^\circ$).

3. Discussion

The present preparation illustrates a general and convenient method for a two-step deoxygenation of carbonyl compounds to olefins.⁶ Related procedures comprise the basic decomposition of p-toluenesulfonylhydrazones,⁷ the hydride reduction of enol ethers,⁸ enol acetates,⁹ enamines,¹⁰ the reduction of enol phosphates (and/or enol phosphorodiamidates) by lithium metal in ethylamine (or liquid ammonia),¹¹ the reduction of enol phosphates by titanium metal under aprotic conditions,¹² the reduction of thioketals by Raney nickel,¹³ and the reduction of vinyl sulfides by Raney nickel in the presence of isopropylmagnesium bromide.¹⁴

Following our first report on the palladium-catalyzed reaction of vinyl triflates with olefins^{15a} (Heck-type reaction), oxidative insertion of palladium(0) into the carbon-oxygen bond of easily available vinyl triflates¹⁶ has proved to be a general method for the generation of σ -vinyl palladium intermediates which can react directly with a variety of olefinic systems,¹⁵ carbon monoxide and alcohols or amines,¹⁷ or 1-alkynes,¹⁸ to give conjugated

dienes, α,β -unsaturated esters or amides, or conjugated enynes, respectively. Palladium-catalyzed coupling of vinyl triflates with organostannanes has also been reported.¹⁹

α -Vinyl palladium triflates are smoothly reduced to alkenes with trialkylammonium formate, usually in high yield.⁶ Some advantages of this reduction procedure should be noted. The trialkylammonium formate-palladium reducing system is very simple to use.²⁰ Clean reduction of vinyl triflates to olefins is observed, no over-reduction being detected. The method is of use in the regioselective synthesis of alkenes and dienes. Ketones, alcohols, ethers, aromatic systems, and presumably a variety of other functional groups are unaffected by the reduction conditions. When the reaction is carried out by using DCOOD, this method allows the regioselective and quantitative introduction of a deuterium atom.

The reaction has been successfully extended to the reduction of aryl triflates to arenes.²¹

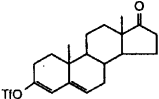

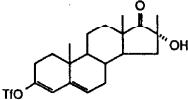

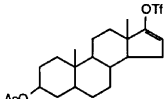
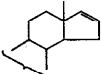
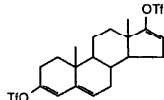
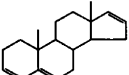
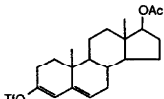
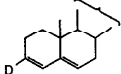
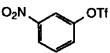

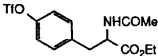
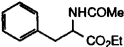
Some selected examples of palladium-catalyzed reduction of vinyl and aryl triflates are summarized in the Table.

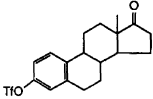
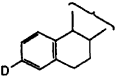
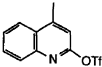

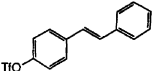
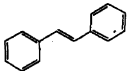
1. Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy.
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TABLE
Palladium-Catalyzed Reduction of Vinyl and Aryl Triflates

Substrate	Catalyst	Product	(% yield)
	$\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$		(81) ⁶
	" "		(93) ⁶
	" "		(85) ⁶
	" "		(95) ⁶
	" "		(87) ⁶
	$\text{Pd}(\text{OAc})_2/\text{DPPF}^b$		(79) ^{21c}
	" "		(94) ^{21c}

Substrate	Catalyst	Product	(% yield)
	$\text{Pd}(\text{OAc})_2/\text{DPPF}^{\text{b}}$		(87) ^{21a}
	" "		(82) ^{21a}
	$\text{Pd}(\text{OAc})_2/(\text{PPh}_3)_2$		(91) ^{21a}

a) DCOOD was used. b) DPPF refers to 1,1'-bis(diphenylphosphino)ferrocene.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cholesta-3,5-diene (8,9); (747-90-0)

Cholesta-3,5-dienyl trifluoromethanesulfonate: Cholesta-3,5-dien-3-ol, trifluoromethanesulfonate (11); (95667-40-6)

2,6-Di-tert-butyl-4-methylpyridine: Pyridine, 2,6-bis(1,1-dimethylethyl)-4-methyl- (9); (38222-83-2)

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

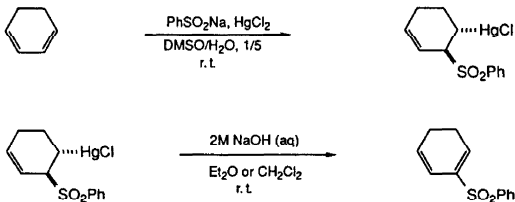
Cholesten-4-en-3-one (8,9); (601-57-0)

Tributylamine (8); 1-Butanamine, N,N-dibutyl- (9); (102-82-9)

Palladium acetate: Acetic acid, palladium (2+) salt (8,9); (3375-31-3)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

2-(PHENYLSULFONYL)-1,3-CYCLOHEXADIENE
(Benzene, (1,5-cyclohexadien-1-ylsulfonyl)-)



Submitted by Jan-E. Bäckvall, Seppo K. Juntunen, and Ove S. Andell.¹

Checked by Willi-Kurt Gries and Larry E. Overman.

1. Procedure

A. trans-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene. A 1-L, one-necked, round-bottomed flask equipped with a large magnetic stirring bar is charged with 32.6 g (120 mmol) of mercury(II) chloride (Note 1), 24.6 g (150 mmol) of sodium benzenesulfinate (Note 2), 80 mL of dimethyl sulfoxide and 400 mL of water. The slurry is initially stirred at room temperature for 2 hr and then 10.6 g (132 mmol) of 1,3-cyclohexadiene (Note 3) is added dropwise under vigorous stirring at room temperature over a period of a few minutes. The reaction mixture is stirred for another 2 hr. The reaction flask is cooled with ice and the solid material collected by filtration using a Büchner funnel (Note 4), washed with 400 mL of water, and dried in a desiccator over calcium chloride at reduced pressure (oil pump), to give 53.0 g (97%) of essentially pure *trans*-3-(phenylsulfonyl)-4-(chloromercuri)cyclohexene (Note 5).

B. 2-(Phenylsulfonyl)-1,3-cyclohexadiene. A 1-L, one-necked round-bottomed flask, equipped with a magnetic stirring bar is charged with 53.0 g (116 mmol) of trans-3-(phenylsulfonyl)-4-(chloromercuri)cyclohexene and 600 mL of diethyl ether (Note 6) at room temperature. The slurry is stirred for 5 min (Note 7) and 175 mL (350 mmol) of a 2 M aqueous solution of sodium hydroxide is added under vigorous stirring (Note 8). The reaction mixture immediately turns black and the vigorous stirring is continued for 30 min (Note 9). The two layers are separated and the aqueous phase is extracted three times with 50-mL portions of diethyl ether. The combined organic layers are filtered through a short column containing 10 g of silica gel and the column is washed with 250 mL of diethyl ether. The ethereal solution is dried over anhydrous magnesium sulfate and filtered, and the solvent is removed at reduced pressure using a rotary evaporator to give 22.5-24.5 g (88-96%) of 2-(phenylsulfonyl)-1,3-cyclohexadiene as a colorless solid (Note 10).

2. Notes

1. Mercury(II) chloride was purchased from Merck & Company, Inc. and used as delivered. The checkers used material purchased from Mallinckrodt Inc.

2. Sodium benzenesulfinate (benzenesulfinic acid, sodium salt) was purchased from Aldrich Chemical Company, Inc. and used without further purification.

3. 1,3-Cyclohexadiene was obtained from Fluka Chemical Corporation and distilled before use. The distillation was performed at ambient temperature and reduced pressure (60-70 mm) and the diene was collected in a flask cooled with liquid nitrogen. The checkers used diene purchased from Aldrich Chemical Company, Inc.

4. A funnel with a fine frit must be used.

5. The crude product melts at 119-123°C and is sufficiently pure for use in the next step. Recrystallization from ethyl acetate provides material melting at 128°C (dec). NMR spectral properties are as follows: ^1H NMR (250 MHz, CDCl_3) δ : 1.92-2.12 (m, 3 H), 2.36-2.51 (m, 1 H), 2.95-3.05 (m, 1 H, H-4), 4.24-4.34 (m, 1 H, H-3), 5.57-5.81 (m, 1 H, =CH), 6.04-6.16 (m, 1 H, =CH), 7.53-7.65 (m, 3 H, ArH), 7.82-7.87 (m, 2 H, ArH); ^{13}C NMR (75 MHz/ CDCl_3) δ : 26.5, 26.7, 44.1, 66.2, 119.6, 129.1, 129.3, 134.2, 135.4, 136.6.

6. The submitters report that dichloromethane can be used also as the solvent with similar results. This modification was not checked.

7. trans-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene is only partly soluble in diethyl ether when the described proportions are used, whereas a clear solution is obtained when dichloromethane is used as solvent.

8. The submitters report that if dichloromethane is used as solvent, 250 mL (500 mmol) of aqueous 2 M sodium hydroxide is added at this point.

9. The submitters report that if dichloromethane is used as solvent, the reaction mixture is stirred for 1.5 hr.

10. The crude product melts at 60-63°C. The spectral properties of 2-(phenylsulfonyl)-1,3-cyclohexadiene are as follows: IR (KBr) cm^{-1} : 3060, 2982, 2923, 2880, 2830, 1585, 1450, 1305, 1150, 1090, 710, 690; ^1H NMR (250 MHz/ CDCl_3) δ : 2.11-2.21 (m, 2 H), 2.35-2.45 (m, 2 H), 5.90-5.97 (m, 1 H, H-4), 6.07 (ddd, 1 H, $J = 9.9, 3.6, 1.8$, H-3), 6.91-6.95 (m, 1 H, H-1), 7.47-7.62 (m, 3 H, ArH), 7.84-7.88 (m, 2 H, ArH); ^{13}C NMR (75 MHz/ CDCl_3) δ : 20.7, 22.3, 118.4, 127.7, 129.1, 130.0, 133.2, 134.8, 138.6, 139.8.

3. Discussion

This procedure^{2,3} illustrates a highly selective and facile method for introducing a phenylsulfonyl group into the 2-position of 1,3-diene systems by using commercially available starting materials. The method can be applied to cyclic as well as acyclic systems giving 2-(phenylsulfonyl)-1,3-dienes. In an alternative synthesis⁴ via condensation of allyl sulfone with aldehyde and subsequent acylation-elimination, the 2-(phenylsulfonyl)-1,3-dienes obtained are limited to acyclic systems.

The procedure described has been applied² to 4-methyl-1,3-pentadiene, 1,3-pentadiene and 1,3-butadiene (Table). Caution must be taken in the handling of the sulfonyldiene products from the two latter dienes. They must be handled and stored in solution since they readily undergo Diels-Alder dimerization when concentrated. For the preparation of 2-(phenylsulfonyl)-1,3-pentadiene, final removal of solvent is never effected, giving a 10 to 50 mM solution of product in the preferred solvent. The solution can be stored at -20°C for several days (<5% dimerization), but the product was usually used within a few hours.

Phenylsulfonyl-1,3-dienes are versatile synthetic intermediates. They can participate in cycloaddition reactions and Michael-type additions^{3,5} leading to adducts which can be further functionalized.³ In the latter case the resulting allylic sulfone can be functionalized by electrophiles, nucleophiles, or both (Figure 1).

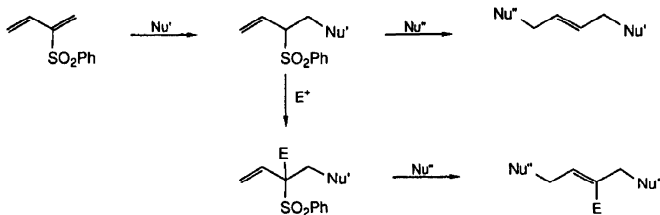


Figure 1

Electron-deficient 1,3-dienes are potentially interesting Diels-Alder dienes. In our study with different kinds of olefins, we observed that 2-(phenylsulfonyl)-1,3-dienes show a duality in their Diels-Alder cycloaddition reactions, giving [4+2] adducts with both electron-deficient and electron-rich olefins.³ This dual reactivity of the 2-(phenylsulfonyl)-1,3-dienes in [4+2] cycloaddition increases the role they can play in organic synthesis.

1. Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

2-(Phenylsulfonyl)-1,3-cyclohexadiene: Benzene, (1,5-cyclohexadien-1-ylsulfonyl)- (11); (102860-22-0)




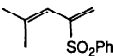

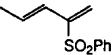


trans-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene: Mercury, chloro[2-(phenylsulfonyl)-3-cyclohexen-1-yl]-, trans- (11); (102815-53-2)

Sodium benzenesulfinate: Benzenesulfinic acid, sodium salt (8,9); (873-55-2)

1,3-Cyclohexadiene (8,9); (592-57-4)

Table

2-(Phenylsulfonyl) 1,3-Dienes from 1,3-Dienes

Olefin	Sulfonyl Diene	Yield (%)
		93 ^a
		67 ^a
		93 ^a
		62 ^b

^a From ref. 2 and 3. ^b A modified procedure, compared to that in ref. 2, was used. Acetone was used as solvent in the first step and the reaction time was longer.

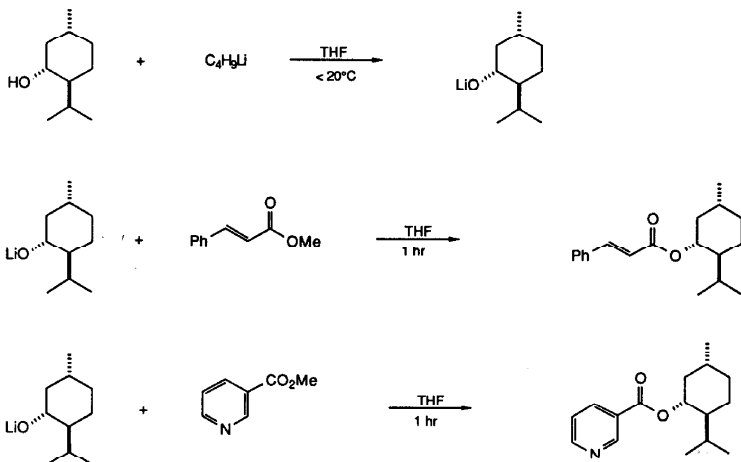
TRANSESTERIFICATION OF METHYL ESTERS OF AROMATIC AND
 α, β -UNSATURATED ACIDS WITH BULKY ALCOHOLS: (-)-MENTHYL

CINNAMATE AND (-)-MENTHYL NICOTINATE

(2-Propenoic acid, 3-phenyl-, 5-methyl-2-(1-methylethyl)cyclohexyl
 ester, [1R-(1 α ,2 β ,5 α)-)

and

(3-Pyridinecarboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl
 ester, [1R-(1 α ,2 β ,5 α)]-)



Submitted by Otto Meth-Cohn.¹

Checked by Gladys Zenchoff, Hubert Maehr, and David Coffen.

1. Procedure

An oven-dried, 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum inlet, an alcohol thermometer and, through the center neck, a pressure-equalizing dropping funnel bearing a calcium chloride drying tube. The apparatus is flushed with argon (Note 1) and the flask is placed in an ice water bath. To the flask are added (-)-menthol (Note 2) (15.63 g, 100 mmol) and 150 mL of dry tetrahydrofuran (THF) (Note 3). To this stirred solution is added dropwise through the dropping funnel butyllithium in hexane (Note 4) (1.60 M, 55 mL, 88 mmol), transferred by syringe, at such a rate that the temperature does not rise above 20°C (about 10 min). When the addition is complete, the methyl ester [either methyl cinnamate (Note 5) (16.21 g, 100 mmol) or methyl nicotinate (Note 5) (13.71 g, 100 mmol)], dissolved in 30 mL of tetrahydrofuran, is added in one lot to the solution and washed in with an additional 20 mL of tetrahydrofuran. The resulting solution, which slowly becomes cloudy, is stirred for another hour (Notes 6 and 7) and then poured into 200 mL of water in a 1-L separatory funnel; the flask is washed out with 100 mL of diethyl ether. The aqueous layer is separated and the organic phase is washed twice with 200 mL of water. After the organic phase is dried with magnesium sulfate, the solvent is removed on a rotary evaporator and the residue is distilled from a 100-mL flask bearing a Vigreux column (Note 8) under reduced pressure (0.1-0.5 mm). After a forerun of 2-3 g (Note 9) the (1R)-(-)-menthyl ester is collected. (1R)-(-)-Menthyl cinnamate distills at 145-147°C (0.2 mm) and is greater than 99% pure by GLC (Note 10). The yield is 22.6-23.9 g (79-83%). (1R)-(-)-Menthyl nicotinate boils at 141-143°C (0.5 mm) and is greater than 99% pure by GLC (Note 10). The yield is 20.1-21.7 g (77-83%).

2. Notes

1. The submitter used a balloon attached by 1" of rubber pressure tubing to the barrel of a plastic disposable syringe bearing a 2"-needle through the septum.

2. (-)-Menthol was obtained from Fluka Chemical Corporation (>99%, puriss. grade) and used directly.

3. Tetrahydrofuran was obtained from BDH Chemicals Ltd. and was distilled from sodium and benzophenone.

4. Butyllithium in hexane was purchased from Lithium Corporation of Europe. The checkers used material supplied by the Aldrich Chemical Company, Inc.

5. Methyl cinnamate (>99%) and methyl nicotinate (>99%) were used as supplied by Fluka Chemical Corporation.

6. The reactions may be monitored by TLC. The submitter used Merck Silica gel pre-coated plates, Silica gel 60 F-254, employing diethyl ether:hexane (1:5) for the cinnamate and (1:1) for the nicotinate transesterifications. After 5 min the reactions are already largely complete. On a small scale, purification by flash chromatography is most effective. R_f times of the reactants are as follows: methyl cinnamate, 0.47; menthyl cinnamate, 0.73; methyl nicotinate, 0.26; menthyl nicotinate, 0.47. Menthol was not visible under ultraviolet light as were the esters, but may be visualized with iodine or phosphomolybdic acid and heat: R_f 0.22 (1:4 ether:hexane).

7. The ice bath may be left in place after all of the reactants are added since the transesterifications are rapid, even below 10°C. If the reaction time is prolonged, only a small difference in product yields results.

8. The submitter used a 120 x 20-mm Vigreux column; the checkers used a 120 x 10-mm column.

9. The forerun contained a mixture of menthol and the methyl ester.

10. Capillary GLC analysis (50 m, OV17, He) gave the following retention times: Menthyl cinnamate 17.5 min (programmed 100-240°C, 5°C/min); menthyl nicotinate 20.2 min (programmed 150-240°C, 5°C/min). The products showed the following properties: Menthyl cinnamate: $[\alpha]_D^{20}$ -57.8° (CHCl₃, *c* 0.20) [lit.² $[\alpha]_D^{25}$ -59.5° (CHCl₃, *c* 7.5)]; ¹H NMR (CDCl₃) δ: 0.6-2.25 (m, 18 H, aliphatic), 4.74 (dt, 1 H, *J* = 9.5 and 5, O-CH), 6.35 (d, 1 H, *J* = 17, olefinic), 7.2-7.6 (m, 5 H, aromatic), 7.83 (d, 1 H, *J* = 17, olefinic). Menthyl nicotinate: $[\alpha]_D^{20}$ -86.8° (CHCl₃, *c* 0.11); ¹H NMR (CDCl₃) δ: 0.6-2.35 (m, 18 H, aliphatic), 5.01 (dt, 1 H, *J* = 4.5 and 10.0, O-CH), 7.40 (ddd, 1 H, *J* = 0.8, 4.8 and 7.8, H-5), 8.32 (dt, 1 H, *J* = 1.8 and 7.8, H-4), 8.81 (dd, 1 H, *J* = 1.8 and 4.8, H-6), 9.30 (dd, 1 H, *J* = 0.8 and 2.1, H-2).

The optical rotations of the products showed a marked dependence on concentration. The submitters found $[\alpha]_D^{20}$ -60.7° (CHCl₃, *c* 0.11) for menthyl cinnamate and $[\alpha]_D^{20}$ -87.9° (CHCl₃, *c* 0.11) for menthyl nicotinate.

3. Discussion

The method described here is based on the general method for such transesterifications.³ The best alcohol is bulky or tertiary, a feature disfavored by most other methods. Thus tert-butyl alcohol, tert-amyl alcohol, lanosterol, cholesterol, fenchol, and borneol are highly effective. If

primary alcohols (e.g., allyl alcohol) are used, it is better to employ 3-5 equiv for an efficient reaction. Alcohols bearing other hetero atoms which form complexes with lithium (e.g., carbohydrate derivatives) prove ineffective in the transesterification.

Methyl esters are always the preferred substrates, conversions being lower with, for example, ethyl esters. Functional groups such as nitro, methoxy, alkenyl and pyridyl are compatible with the reaction conditions. Diesters can only be effective if bis-transesterification is desired, when an excess of the alcohol (e.g., 3-5 equiv) is necessary. Methyl acrylate tends to polymerize under the reaction conditions, but the use of an excess of the ester (3-5 equiv) and lower temperatures (-10°C) allows efficient isolation of the required ester.

Organolithium compounds other than butyllithium can be used with no change in the reaction efficiency; reduction of the molar ratio of organolithium to alcohol merely slows the transesterification. Even when one-sixth of an equivalent is used, efficient but slow transesterification occurs. In no case has it been found necessary to leave reactions longer than 18 hr or to use temperatures higher than ambient. Ether solvents are far more effective than hydrocarbons, in which slower reactions occur.

There are very few known methods for transesterifications using bulky alcohols. Thiol esters undergo ready mercury(II) trifluoroacetate-catalyzed transesterifications with tert-butyl alcohol.⁴ Potassium tert-butoxide in the presence of 4-Å molecular sieves converts certain dimethyl malonates into methyl tert-butyl malonates.⁵ The majority of published transesterification methods involve the use of primary or occasionally secondary alcohols and a catalyst, and either require a large excess of one reactant or continuous removal of a low boiling component in the equilibrium. Catalysts include

acids such as sulfuric⁶ or p-toluenesulfonic acid,⁷ Lewis acids such as boron tribromide,⁸ or bases such as alkoxides.^{4,9} Neutral catalysts, in particular titanates,¹⁰ and potassium cyanide¹¹ have also been used.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

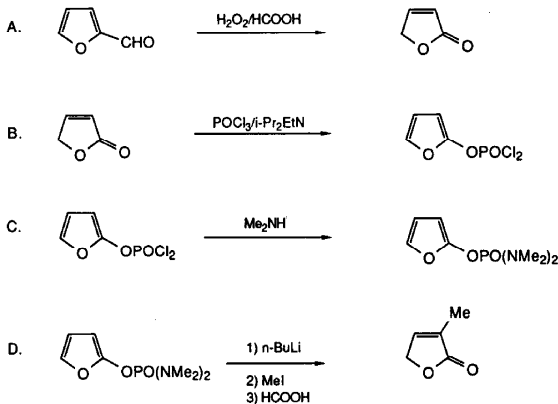
(-)-Menthyl cinnamate: Menthyl cinnamate, (-)- (8); 2-Propenoic acid, 3-phenyl-, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1 α ,2 β ,5 α)]- (9); (16205-99-5)

(-)-Menthol: Menthol, (-)- (8); Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1 α ,2 β ,5 α)]- (9); (2216-51-5)

Methyl cinnamate: Cinnamic acid, methyl ester (8); 2-Propenoic acid, 3-phenyl-, methyl ester (9); (103-26-4)

Methyl nicotinate: Nicotinic acid, methyl ester (8); 3-Pyridinecarboxylic acid, methyl ester (9); (93-60-7)

3-METHYL-2(5H)-FURANONE
(2(5H)-Furanone, 3-methyl-)



Submitted by Jan H. Näsman.¹

Checked by Alan T. Johnson and James D. White.

1. Procedure

Caution. Hydrogen peroxide attacks the skin and may decompose violently. The first step should be carried out behind a safety screen, and the operator should wear safety glasses and rubber gloves. Air must not be admitted to the hot distillation residue in step 2.

A. *2(5H)-Furanone.* A 6-L, three-necked, round-bottomed flask equipped with two condensers, a dropping funnel and a 12 x 55 mm magnetic stirring bar is charged with 480 g (5 mol) of furfural (Note 1) and 2.0 L of methylene

chloride. The addition of 200 g of sodium sulfate (Note 2) and 150 g of N,N-dimethylethanolamine (Note 3) in one portion each is followed immediately by 460 g of formic acid (Note 4), carefully added in portions over a period of 2 min, after which 100 mL of 30% hydrogen peroxide (Note 5) is added in one portion. The mixture is stirred vigorously. After 5 min the mixture will reflux and another 800 mL of 30% hydrogen peroxide is added dropwise during 9 hr (Note 6) while stirring is continued. When the addition is complete the mixture is vigorously stirred as long as it refluxes and then stirred gently overnight. The organic phase is separated, and the water phase is extracted with the 200 mL of methylene chloride that is used to wash out residues from the reaction flask.

The methylene chloride-phase is washed with two 150-mL portions of saturated sodium disulfite solution (Note 7) and dried over magnesium sulfate and sodium sulfate. After a negative peroxide test (Note 8) the solvent is removed. The crude product (255 g) is fractionated through a 30-cm Vigreux column. The material boiling at 85-95°C (13 mm) is collected to give 210 g of butenolide, which is yellow because of some high boiling residues. Redistillation through the 30-cm Vigreux column and collection of the material boiling at 100-102°C (30 mm) or 95-97°C (19 mm) or 89-91°C (16 mm) or 79-81°C (9 mm), gives colorless butenolide. In this way 170.2 g (41%) of pure butenolide is obtained.

B. Furyl phosphorodichloridate. A 1-L flask, protected from moisture by a calcium chloride tube, is charged with 42 g (0.5 mol) of 2(5H)-furanone, 85 g (0.55 mol) of phosphoryl chloride and 100 mL of methylene chloride. A solution of 65 g (0.5 mol) of ethyldiisopropylamine in 60 mL of methylene chloride is added dropwise during 4 hr at ambient temperature (Note 9). The resulting mixture is stirred overnight (12 hr), after which 6.5 g of the amine

in 10 mL of methylene chloride is added in one portion and stirring is continued for 20 hr (Note 10). The solvent is removed on a rotary evaporator and 200 mL of dry ether (Note 11) is added cautiously, followed by 100 mL of pentane (in that order), to the dark residue to precipitate the amine hydrochloride. The flask is stoppered and shaken for 1-2 min. The hydrochloride is filtered by suction and washed immediately with 100 mL of dry ether and 200 mL of pentane or petroleum ether (Note 12). The bottle is tightly stoppered and the filtrate is allowed to stand in the refrigerator (+4°C) overnight. The clear brown ethereal phase is decanted from a dark lower phase, and the solvent is evaporated. The residue (~ 100 g) is distilled at the water pump. In order to obtain pure, color-stable, yellow dichloridate it is usually necessary to distill it twice. The first distillation is done rapidly, collecting the material that boils at 73-98°C (9 mm) to give 65-75 g of product, which usually darkens within a few days (Notes 13 and 14). Redistillation (Note 15), collecting the material that boils at 91-93°C (22 mm) or 88-90°C (16 mm) or 73-76°C (9 mm), gives 60-65 g of pure product (Note 16). The yield is 60-65%.

C. *Furyl N,N,N',N'-tetramethyldiamidophosphate.* To 180 mL of dry diethyl ether, chilled to -30°C, is added 56.7 g (4.2 equiv) (1.26 mmol) of dimethylamine (Note 17). This solution is added during 1-2 hr from a double jacketed dropping funnel, protected from moisture by a calcium chloride-tube and connected to a cryostat regulated to -30°C, to a stirred mixture (Note 18) of 60 g (0.30 mol) of the freshly distilled furyl phosphorodichloridate and 250 mL of ether in a two-necked, 1-L flask equipped with a condenser, protected from moisture by a calcium chloride-tube and connected to the cryostat. This flask is chilled in an ice bath during the addition of the first two equivalents of the dimethylamine. After the addition of

dimethylamine is complete, stirring is continued for 20 hr while the mixture is warmed on a water bath at 35°C. The hydrochloride which forms is carefully filtered off with suction and washed with two 70-mL portions of dry ether. The combined ether phases are evaporated to give ~65 g (99%) of crude product. Distillation, discarding a yellow forerun and collecting the fraction boiling at 149-152°C (20 mm) or 131-134°C (7 mm) (Note 19), affords 52-58 g (79-88%) of pure material (Note 20).

D. *3-Methyl-2(5H)-furanone*. To 10.9 g (50 mmol) of furyl tetramethyldiamidophosphate in 90 mL of tetrahydrofuran (THF) (Note 21), chilled to -75°C, is added 21.9 mL (55 mmol) of a 2.51 M hexane solution of butyllithium (Note 22) at a rate (6-10 min) such that the temperature reaches -60°C but does not exceed this temperature. The resulting mixture is chilled to -75°C for 10 min; then 8.9 g (63 mmol) of methyl iodide in 20 mL of tetrahydrofuran is added with a syringe during 7-8 min (Note 23) so that the temperature does not rise above -55°C. After the addition is complete, the temperature is raised to 0°C and the mixture is concentrated to ca. 40 mL. Water (30 mL) and ethyl acetate (50 mL) are added, the phases are separated, and the dark inorganic phase is extracted with two 50-mL portions of ethyl acetate. The combined, yellow organic phases are washed with brine and dried over magnesium sulfate. The solvent is evaporated to give 10.5 g of crude 2-(3-methylfuryl) tetramethyldiamidophosphate, which need not be purified for the next reaction (Note 24).

To the phosphate in a 250-mL flask on a water bath at 25°C (Note 25) is added 20 mL of 98-100% formic acid (Note 26) and the resulting mixture is stirred until bubbling has ceased (30-40 min). Benzene (50 mL) is added and most of the excess formic acid is removed on an evaporator. To the residue are added 50 mL of ethyl acetate and 30 mL of a sodium chloride-sodium

carbonate solution (Note 27). The organic phase is washed twice with the latter solution (i.e., a total of 3 x 30 mL), the combined inorganic phases are extracted once with 50 mL of ethyl acetate, the combined organic phases are dried over magnesium sulfate, the solvent is removed and the product is distilled to give 3.2 g (64%) of 3-methyl-2(5H)-furanone, bp 97-101°C (19 mm).

2. Notes

1. Practical grade furfural from Fluka Chemical Corporation or Aldrich Chemical Company, Inc. was used without any purification. Very dark furfural can be used, but it foams at the beginning of the reaction and leads to lower yields.

2. Sodium sulfate is used to salt-out the water phase; brine is not effective. The yield without the sulfate is 5-10% lower.

3. N,N-Dimethylethanolamine (99% pure) was obtained from EGA CHEMIE or Aldrich Chemical Company, Inc. The role of the compound is to isomerize any 2(3H)-furanone formed.

4. Formic acid (98-100%), obtained from Merck & Company, Inc., was used.

5. "Perhydrol" (30%), obtained from Merck & Company, Inc., gave reproducible results without efforts to determine the activity of the peroxide. An excess is used.

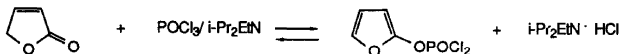
6. The process is a fine balance between oxidation and isomerization of the initially formed 2(3H)-furanone. Longer addition times produce better yields; however, the benefit is of marginal value.

7. Sodium disulfite, $\text{Na}_2\text{S}_2\text{O}_5$, from Merck & Company, Inc. was used. The saturated solution of disulfite should be the lower phase.

8. The mixture is tested for peroxide as follows: Prepare an approximately 1% solution of ferrous ammonium sulfate. Transfer 5 mL to each of two test tubes and add 0.5 mL of 0.5 M sulfuric acid and 0.5 mL of 0.1 M potassium thiocyanate solution to each tube. Add 5 mL of the methylene chloride solution to one of the test tubes and shake well. The aqueous phase in the methylene chloride tube should not develop a brown red color when examined parallel to the blank.

9. Phosphoryl chloride from Fluka Chemical Corporation or Aldrich Chemical Company, Inc., and methylene chloride (purum) from Merck & Company, Inc., were used. Unless the contents of a freshly opened bottle were used, methylene chloride was distilled from phosphorus pentoxide (20 g/L) before use. The amine (Fluka or Aldrich) was distilled from and stored over potassium hydroxide. The best yields were obtained with once-recovered amine.

10. The reaction



is reversible. In order to obtain pure (97-98%) dichloridate it is essential to add the 6.5 g of amine after the first equivalent has reacted.

11. Ordinary diethyl ether is stored over calcium chloride for 36 hr, filtered, and dried over sodium wire.

12. The use of more pentane or petroleum ether gave a product of better stability and purity.

13. Once-distilled product was usually not color-stable for prolonged periods.

14. The distillation flask is allowed to cool before air is passed into it. A vigorous polymerization may occur if air is passed into the hot residue, which may be safely discarded after the addition of acetone (an exothermic, but easily controlled reaction).

Spectroscopic data for furyl phosphorodichloridate are as follows: ^1H NMR (60 MHz, CDCl_3 , TMS) δ : 5.85 (m, 1 H, furan-H3), 6.30 (m, 1 H, furan-H4), 7.05 (m, 1 H, furan-H5); ^{13}C NMR (CDCl_3 , TMS) δ : 92.5 ($^3\text{J}_{\text{PC}} = 7$, furan-C3), 111.5 ($^4\text{J}_{\text{PC}} = 3$, furan-C4), 137.1 ($^4\text{J}_{\text{PC}} = 3$, furan-C5), 147.9 ($^2\text{J}_{\text{PC}} = 12$, furan-C2). MS m/e (rel. int.): 202 (16), 200 (26), 119 (4), 117 (6), 83 (100), 55 (31); M^+ 201.9160: Calcd 201.9167 for $\text{C}_4\text{H}_3\text{Cl}_2\text{O}_3\text{P}$; obsv 199.9195: Calcd 199.9197; IR cm^{-1} : 1610 (s), 1300 (s), 980 (s), 890, 870; Anal. Calcd for $\text{C}_4\text{H}_3\text{Cl}_2\text{O}_3\text{P}$: C, 23.9, H, 1.5; Found: C, 23.8, H, 1.5.

15. Pure pale yellow dichloridate is stable for months without extensive change of color if stored in well-stoppered bottles in the refrigerator.

16. The purity of this product is 97-98%. It contains some butenolide; therefore an excess of dimethylamine is used in the subsequent step.

17. Dry dimethylamine from Fluka Chemical Corporation or MC and B Manufacturing Chemists was used as delivered.

18. A 12 x 55 mm heavy magnetic stirring bar is used for good stirring.

19. The monochloroamidate distills at 123°C (9 mm) and is identified in the ^1H NMR by its $^3\text{J}_{\text{PH}} = 13.5$. *Distill slowly in the beginning!* The purity of the product is 99+%. Redistill if a dark yellow color develops; however, this color does not preclude successful lithiation.

20. The distilled diamide is a pale yellow oil at room temperature; it freezes in the refrigerator (+4°C) if seeded within some hours. The first spontaneous crystallization took several weeks. It can also be obtained as snow white crystals from diisopropyl ether/hexane, mp 15-16°C.

Spectroscopic data for furyl tetramethyldiamidophosphate are as follows: ^1H NMR (400 MHz, CDCl_3 , TMS) δ : 2.71 (d, 12 H, $^3J_{\text{PH}} = 10$, two $\text{N}(\text{CH}_3)_2$), 5.62 (m, 1 H, furan-H3), 6.28 (m, 1 H, furan-H4), 6.95 (m, 1 H, furan-H5); ^{13}C NMR (15.03 MHz, CDCl_3 , TMS) δ : 151.9 (d, $^2J_{\text{PC}} = 6$, furan-C2), 134.5 (s, furan-C5), 111.3 (s, furan-C4), 88.8 (d, $^3J_{\text{PC}} = 4$, furan-C3), 36.6 (d, $^2J_{\text{PC}} = 4$, $\text{N}(\text{CH}_3)_2$). Note that multiplicities s and d refer to C-P coupling. MS m/e (rel. int.): 218 (6), 136 (6), 135 (100), 127 (2), 111 (2), 92 (7), 90 (2), 83 (4), 69 (3). M^+ at 218.0822: Calcd 218.0820 for $\text{C}_8\text{H}_{15}\text{N}_2\text{O}_3\text{P}$; IR cm^{-1} : 2900, 2800, 1610, 1300, 990, 960.

21. Tetrahydrofuran (Merck) was distilled from sodium-benzophenone ketyl prior to use.

22. Butyllithium was obtained from Aldrich Chemical Company, Inc., and methyl iodide from Merck & Company, Inc. Butyllithium was titrated with phenanthroline as indicator prior to use according to the method of Watson and Eastham.¹¹ Fresh alkoxide-free butyllithium should be used to ensure pure product.

23. Methyl iodide should be added carefully in the beginning when the reaction mixture is mostly solid.

24. The phosphate can be crystallized from diisopropyl ether/hexane at -20°C in 80-85% yield; mp $42-44^\circ\text{C}$.

Spectroscopic data for 2-(3-methylfuryl) tetramethyldiamidophosphate are as follows: ^1H NMR (400 MHz, CDCl_3 , TMS) δ : 1.95 (dxt, 3 H, $J = 0.4$ and 2.2 CH_3), 2.73 (d, 12 H, $^3J_{\text{PH}} = 10.2$, two $\text{N}(\text{CH}_3)_2$), 6.16 (dxdxq, 1 H, $J = 0.4$ and 2.2, furan-H4), 6.91 (dxdxq, 1 H, $J = 0.4$ and 2.2, furan-H5); ^{13}C NMR δ : 8.4 (sxq, CH_3), 36.6 (dxq, $^2J_{\text{PC}} = 4$, $\text{N}(\text{CH}_3)_2$), 98.7 (dxs, $^3J_{\text{PC}} = 5$, furan-C3), 113.8 (dxd, $^4J_{\text{PC}} = 2$, furan-C4), 133.9 (dxd, $^4J_{\text{PC}} = 2$, furan-C5), 147.8 (dxs, $^3J_{\text{PC}} = 8$, furan-C2); multiplicities underlined in the ^{13}C -spectrum

refer to C-P coupling, the other to C-H coupling; MS m/e (rel. int.): 232 (7), 135 (100), 97 (3), 92 (5), M^+ at 232.0980: Calcd 232.0977 for $C_9H_{17}N_2O_3P$: Calcd for $C_9H_{17}N_2O_3P$: C. 46.55, H. 7.33, N. 12.07; Found: C. 46.5, H, 7.6, N, 12.0.

25. The water bath can be removed after 5 min. The reaction is vigorous in the beginning and chilling is necessary to avoid formation of dimethylformamide (DMF), which is formed at elevated temperatures.

26. Formic acid (98-100%), obtained from Merck & Company, Inc., was used.

27. *Warning:* CO_2 evolution. The sodium chloride-sodium carbonate solution was prepared from 185 g of sodium chloride and 110 g sodium carbonate dissolved in water to give a total volume of 1 L.

3. Discussion

The preparation of 2(5H)-furanone is the scaled-up and slightly modified procedure² based on the report of Badovskaya that furfural is oxidized with performic acid to give a mixture of furanones.³ The preparation here is improved by the use of N,N-dimethylaminoethanol as a catalyst for the isomerization of 2(3H)-furanone to 2(5H)-furanone. The complex between this amino alcohol and formic acid does not enter the organic phase during workup and the product is thus easily isolated simply by evaporation of the solvent.

The hitherto preferred method for preparation of the butenolide is that of Price and Judge,⁴ which can be modified (by extraction of the bromolactone with methylene chloride and elimination of hydrogen bromide with triethylamine or preferably with diisopropylethylamine in toluene at 70°C) to give routinely 60% or greater overall yield on a 6-mol scale. However, the large amount of

hydrogen bromide evolved is sometimes a nuisance, especially to inexperienced workers. The method reported here is fast, independent of scale (0.1-6 mol tried), the starting materials are cheap, and the product is easily isolated.

Substituted furfurals do not react at a synthetically-useful rate when formic acid/hydrogen peroxide is used. This suggests that the reaction takes place in the water phase and that substituted furfurals enter this phase only with difficulty.

The preparation of furyl phosphorodichloridate is based upon a method to prepare 2-chlorofuran (16% yield, Horni, Näsman unpublished). Later the preparation was extended to a general method to prepare furyl esters from carboxylic acid chlorides lacking α -hydrogens and alkyl furyl carbonates from primary (other than methyl) and secondary alkyl chloroformates.⁵ Phosphoryl chloride was the only acid chloride except carbon analogues found to give a furyl ester by the amine-catalyzed reaction.

Regioselective β -metallation of π -excessive five ring heterocycles is not a novel reaction.⁶ Oxazoline⁷ and pyridine⁸ as well as carboxylate⁹ and carboxamide¹⁰-substituted heterocycles have been lithiated. From the point of synthetic utility thiophenes have been shown to be useful substrates after careful optimization of reaction conditions; furans have been of less utility.

The generation of 2-(3-lithio)furyl tetramethyldiamidophosphate ($> 95\%$) in tetrahydrofuran with a slight excess of butyllithium is a reliable procedure. The reagent usually forms a precipitate (active) when stored for prolonged times (3-12 hr) at -80°C and less than 35 mL of tetrahydrofuran/10 mmol of reagent is used.⁶ The reagent darkens when warmed to -30°C . The reagent has been used on 100-mmol scales with no difficulties in methylation with methyl iodide. Methyl iodide is a very good electrophile for the reagent, whereas ethyl iodide does not react. Other good substrates for this

unmodified reagent are ketones, aldehydes, and chloromethyl ethers. Alkylation is difficult unless strongly activated substrates are used. For example, benzyl chloride is unreactive, benzyl bromide reacts but not completely, and the corresponding iodide gives a complex mixture.

The reagent must be added to the electrophile when the leaving group is an alkoxide. For example, quenching with MeOD on larger scales yields products labelled also in the 5-position, whereas reverse addition with good stirring does not.

The furan products can be purified by flash chromatography¹² and should be used at once. A mixture of ethyl acetate and methylene chloride is a good solvent system for flash chromatography. Small residues of silica tend to partly decompose these furans within two weeks. The products are hygroscopic. Diisopropyl ether-diethyl ether-hexane is a useful solvent system for recrystallization of solid furans.

The formic acid reaction to convert furans to butenolides seems to be general, although heating may be necessary for acceptor-substituted furans; dimethylformamide (DMF) is then a byproduct.

In conclusion, furyl N,N,N',N'-tetramethylamidophosphate is the precursor to the d²-synthon 1 for butenolide, which is difficult to generate by direct or other indirect methods;¹³ however, see reference 14 for a metal-halogen exchange reaction of 3- or 4-bromo-2-methoxy- or 2-trimethylsiloxyfurans.



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Methyl-2(5H)-furanone: 2-(5H)-Furanone, 3-methyl- (8,9); (22122-36-7)

2(5H)-Furanone (8,9); (497-23-4)

Furfural: 2-Furaldehyde (8); 2-Furancarboxaldehyde (9); (98-01-1)

N,N-Dimethylethanolamine: Ethanol, 2-(dimethylamino)- (8,9); (108-01-0)

Furyl phosphorodichloridate: Phosphorodichloridic acid, 2-furanyl ester (12);
(105262-70-2)

Phosphoryl chloride (8,9); (10025-87-3)

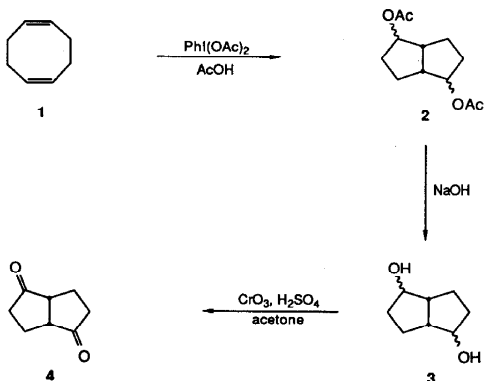
Ethyl-diisopropylamine: Triethylamine, 1,1'-dimethyl- (8); 2-Propanamine,

N-ethyl-N-(1-methylethyl)- (9); (7087-68-5)

Furyl N,N,N',N'-tetramethyldiamidophosphate: Phosphorodiamidic acid,
tetramethyl-, 2-furanyl ester (12); (105262-58-6)

2-(3-Methylfuryl) tetramethylamidophosphate: Phosphorodiamidic acid,
tetramethyl-, 3-methyl-2-furanyl ester (12) (105262-59-7)

INTRAMOLECULAR CYCLIZATION OF *cis,cis*-1,5-CYCLOOCTADIENE USING
HYPERVALENT IODINE: BICYCLO[3.3.0]OCTANE-2,6-DIONE
(1,4-Pentalenedione, hexahydro-)



Submitted by Robert M. Moriarty,¹ Michael P. Duncan,¹
 Radhe K. Vaid,¹ and Om Prakash.²
 Checked by Deng Bing and Ekkehard Winterfeldt.

1. Procedure

A. *2,6-Diacetoxycyclo[3.3.0]octane*, 2, (Notes 1 and 2). An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar, reflux, condenser, and drying tube (Drierite), is charged with iodosobenzene diacetate (IBD) (100 g, 0.31 mol) and 300 mL of glacial acetic acid. To this stirred mixture, 25 g (0.23 mol) of *cis,cis*-1,5-cyclooctadiene (COD) is

added. The resulting mixture is then heated to reflux for 16 hr (Note 3) at which time the colorless solution has become brown-orange. At the end of this time the acetic acid is evaporated using a rotary evaporator (15 mm). Reduced-pressure distillation (74-84°C/0.060 mm) yields 29.1-30.5 g (56-58%) of 2, 2,6-diacetoxibicyclo[3.3.0]octane, as a pale yellow liquid (lit.³ bp 84-88°C at 0.2 mm) (Note 4).

B. *Bicyclo[3.3.0]octane-2,6-diol*, 3, (Note 5). An ice-cooled aqueous 10% solution of sodium hydroxide (100 mL) is placed in a 250-mL, round-bottomed flask equipped with a magnetic stirring bar and stopper. To this ice-cooled solution 27.8 g of diacetate 2 (0.123 mol) is added dropwise over a few minutes. The cooled solution is slowly allowed to warm to room temperature (1 hr) and stirring is continued for 15 hr, at which time the colorless solution has become yellow-orange (Note 6).

The reaction mixture is then extracted continuously with ether for 3 days. After extraction the ether is removed by rotary evaporation. The crude viscous liquid which results after evaporation (Note 7) is distilled (Note 8) under reduced pressure (106-111°C/0.06 mm) (lit.³ bp 90-96°C at 0.3 mm) to yield 14.5-16.2 g (83-93%) of 3, pure bicyclo[3.3.0]octane-2,6-diol, as a yellow viscous liquid (Note 9).

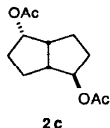
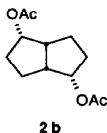
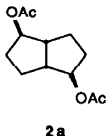
C. *Bicyclo[3.3.0]octane-2,6-dione*, 4, (Note 10). Diol 3, 12.6 g (0.089 mol), is placed in a 250-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. Acetone (125 mL) is added and the mixture is cooled to 0°C. A 2.7-M solution of Jones reagent (Note 11) (70 mL) is slowly added dropwise over 10 min at 0°C. The solution is allowed to warm slowly to room temperature (1 hr) and stirring is continued for an additional 15 hr.

After 15 hr the acetone is removed on a rotary evaporator and water (125 mL) is added. The dark green aqueous mixture is extracted continuously with ether for 3 days. The ether is removed by rotary evaporation which results in a yellow oil. The oil is then distilled under reduced pressure (74-79°C/0.06 mm) to yield analytically pure bicyclo[3.3.0]octane-2,6-dione, 4, (6.4-7.1 g, 52-50%) as a white crystalline solid mp 45-46°C; lit.⁴ mp 45.1-46.3°C (Notes 12 and 13).

2. Notes

1. cis,cis-1,5-Cyclooctadiene (COD) and iodosobenzene diacetate (IBD) are purchased from Aldrich Chemical Company, Inc.

2. The diacetate (2) is a mixture of three difficultly separable stereoisomers [the di-exo-diacetate (2a), di-endo-diacetate (2b), and the exo-endo-diacetate (2c)]. The major isomer is the di-exo-diacetate (2a) based on ¹³C-NMR of the known di-exo-diol, see (Note 9).



3. This solution of iodosobenzene, acetic acid, and cis,cis-1,5-cyclooctadiene should continue to be stirred and should not be allowed to react for more than 20 hr (at refluxing temperature) to prevent decomposition of the product diacetate.

4. The ¹H NMR spectrum (CDCl₃) is as follows δ: 1.60 (m, 8 H, CH₂), 1.97 (s, 6 H, OAc), 2.55 (br, s, 2 H, CH), 4.90 (br, s, 2 H, CHOAc). The IR spectrum (neat) shows a carbonyl peak at 1738 cm⁻¹.

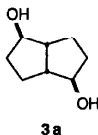
5. This procedure for the preparation of the diol is an adapted version of that by Cantrell and Strasser.³ It is a superior procedure to that of Crandall and Mayer.⁵

6. The checkers monitored the reaction by TLC using ethyl acetate as the developing solvent.

7. This viscous liquid (3) is easily transferred to a distilling flask by using acetone.

8. The use of a heat gun aids the distillation because the product is extremely viscous.

9. The ¹H NMR spectrum (CDCl₃) is as follows δ: 1.70 (m, 8 H, CH₂), 2.61 (m, 2 H, CH), 3.05 (s, 2 H, OH), 3.90 (m, 2 H, CHOH). The IR spectrum shows a broad peak at 3500 cm⁻¹. The major peaks in the ¹³C NMR spectrum (CDCl₃) are δ: 27.41 (C-4), 33.81 (C-3), 50.64 (C-1), 79.54 (C-2). The ¹³C NMR indicates that the major stereoisomer is 3a, the exo, exo-2,6-dihydroxycis-bicyclo[3.3.0]octane [lit.⁶ ¹³C NMR δ: 27.8 (C-4), 34.2 (C-3), 51.0 (C-1), 79.9 (C-2)].



10. Other oxidation procedures were used, e.g., pyridinium chlorochromate (Corey's reagent),⁷ and dipyridine Cr(VI) oxide (Collins' reagent),⁸ but did not produce yields comparable to the Jones method.

11. Jones reagent was prepared by the method in Fieser and Fieser:⁹ Dissolve 13.36 g of chromium trioxide in 11.5 mL of concd sulfuric acid, and carefully dilute this cooled solution (0°C) with water to 50 mL.

12. The ^1H NMR spectrum (CDCl_3) is as follows δ : 2.23 (m, 8 H, CH_2), 3.00 (m, 2 H, CH). The IR spectrum (Nujol) shows a carbonyl peak at 1745 cm^{-1} .

13. GLC analysis shows that the product is contaminated by small amounts of diol. If desired, purer material could be obtained by sublimation at $35\text{--}40^\circ\text{C}/0.01\text{ mm}$ onto a cold finger kept at 0°C .⁴

3. Discussion

The preparation of bicyclo[3.3.0]octane-2,6-dione has been accomplished by intermolecular reactions,^{4,10} intramolecular reactions,^{3,11} and degradation reactions.^{5,12}

Bicyclo[3.3.0]octane-2,6-dione has been known since 1934,¹⁰ but extant procedures for large-scale multi-gram synthesis of this versatile intermediate are cumbersome, except for the recently published results of Hagedorn and Farnum.⁴ Whitesell and Matthews⁶ have shown that bicyclo[3.3.0]octanes are valuable intermediates for the total synthesis of natural products.

We now report a simple, three-step synthesis of the dione, which uses simple procedures and inexpensive starting materials, to procure multigram amounts of bicyclo[3.3.0]octane-2,6-dione in reasonable yields.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

Bicyclo[3.3.0]octane-2,6-dione: 1,4-Pentalenedione, hexahydro- (8,9);
(17572-87-1)

cis,cis-1,5-Cyclooctadiene: 1,5-Cyclooctadiene, (Z,Z)- (8,9);
(1552-12-1)

2,6-Diacetoxycyclo[3.3.0]octane: 1,4-Pentalenediol, octahydro-, diacetate
(8,9); (17572-85-9)

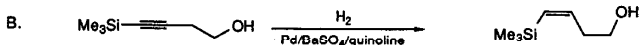
Iodosobenzene diacetate: Benzene, (diacetoxyiodo)- (8);

Iodine, bis(acetato-0)phenyl- (9); (3240-34-4)

Bicyclo[3.3.0]octane-2,6-diol: 1,4-Pentalenediol, octahydro- (8);

1,4-Pentalenediol, octahydro-, (1 α ,3 α ,4 α ,6 α)- (10); (17572-86-0)

(Z)-4-(TRIMETHYLSILYL)-3-BUTEN-1-OL
(3-Buten-1-ol, 4-(trimethylsilyl)-, (Z)-)



Submitted by Larry E. Overman, Mark J. Brown, and Stephen F. McCann.¹

Checked by Ronald C. Newbold and Andrew S. Kende.

1. Procedure

A. Preparation of 4-(trimethylsilyl)-3-butyne-1-ol. A flame-dried, three-necked, 2-L, round-bottomed flask is fitted with a 1-L pressure equalizing addition funnel, a mechanical stirrer, and a nitrogen inlet. The flask is flushed with dry nitrogen and charged with 3-butyne-1-ol (Note 1) (freshly distilled, 31.4 g, 0.448 mol) and 900 mL of anhydrous tetrahydrofuran (Note 2). The stirred solution is cooled to 0°C under nitrogen and to it is added over 1 hr a solution of ethylmagnesium bromide in tetrahydrofuran (493 mL of 2.0 M soln, 0.986 mol) (Note 1). The resulting heterogeneous mixture is rapidly stirred at 0°C for 1 hr, allowed to warm to room temperature for 1 hr, and then recooled to 0°C. To this mixture is slowly added over 30 min with rapid stirring freshly distilled (Note 3) chlorotrimethylsilane (125 mL, 0.986 mol). The mixture is stirred for 1 hr at 0°C and allowed to warm to room temperature over 1-2 hr. The entire reaction mixture is poured slowly with

rapid stirring into a 4-L Erlenmeyer flask which contains 1 L of ice-cold 3 M hydrochloric acid, and stirred at 25°C for an additional 2 hr. The organic phase is separated and the aqueous phase is extracted with three 200-mL portions of ether.

The combined organic phases are washed with two 200-mL portions of water, four 200-mL portions of saturated sodium bicarbonate solution, and two 200-mL portions of saturated sodium chloride. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure at room temperature using a rotary evaporator. The crude product is distilled through a short-path distillation apparatus under reduced pressure to give 45.2 g (0.318 mol, 71% yield) of 4-(trimethylsilyl)-3-butyne-1-ol, bp 78-79°C (10 mm), as a colorless liquid (Notes 4 and 5).

B. Preparation of (Z)-4-(trimethylsilyl)-3-buten-1-ol. A dry, 250-mL, round-bottomed flask with a stirring bar is charged with 8.84 g (0.062 mol) of 4-(trimethylsilyl)-3-butyne-1-ol, 0.4 g of 5% palladium on barium sulfate (Note 6), 0.45 g of synthetic quinoline (Note 7) and 78 mL of methanol. The flask is placed on a hydrogenation apparatus equipped with a gas burette, and the stirred mixture is thoroughly purged with nitrogen. The nitrogen is then replaced by hydrogen and the reaction mixture is stirred at atmospheric pressure and room temperature until 1.46 L (0.065 mol) of hydrogen is consumed. The flask is flushed with nitrogen and the solution is filtered through a thick pad of Celite. The filtrate is concentrated on a rotary evaporator at room temperature to afford 10-15 mL of an oil, which is diluted with 150 mL of ether. The ether solution is thoroughly washed once with 200 mL of ice-cold 0.2 M sulfuric acid, then once with 20 mL of 5% sodium bicarbonate solution. The ether layer is dried over anhydrous magnesium sulfate, filtered, and concentrated to yield 8.4 g (0.058 mol) of the crude

buten-1-ol (Note 8). Short path distillation under reduced pressure gives 7.60 g (0.0527 mol, 85% yield) of (Z)-4-(trimethylsilyl)-3-buten-1-ol, bp 95-100°C (25 mm) as a colorless liquid (Notes 9 and 10).

2. Notes

1. The reagents, 3-butyne-1-ol and 2.0 M ethylmagnesium bromide in tetrahydrofuran, were purchased from Aldrich Chemical Company, Inc. The ethylmagnesium bromide concentration can be easily checked by titration with menthol using 1,10-phenanthroline as indicator.²

2. Tetrahydrofuran was distilled from sodium and benzophenone under a nitrogen atmosphere.

3. Chlorotrimethylsilane was purchased from Aldrich Chemical Company, Inc., and was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use.

4. The product, 4-(trimethylsilyl)-3-butyne-2-ol, shows the following proton NMR spectrum at 300 MHz in CDCl₃ δ : 0.03 (s, 9 H, SiCH₃), 1.8 (broad s, 1 H, OH), 2.47 (t, 2 H, CH₂), 3.67 (m, 2 H, CH₂OH); and infrared spectrum (neat) cm⁻¹: 3350 (very broad), 2178, 1250, 1031, 894, 842, 760.

5. Similar yields can be obtained in this silylation by using the chloromagnesium salt (from butylmagnesium chloride) as described in *Org. Synth.* 1987, 65, 61.

6. The 5% palladium on barium sulfate was purchased from Engelhard Industries, Newark, NJ.

7. Synthetic quinoline was purchased from Aldrich Chemical Company, Inc. and was distilled prior to use.

8. The proton NMR spectrum of the crude buten-1-ol was essentially identical to that of the distilled product, except for traces of solvent. This crude silylbuten-1-ol was of sufficient purity for the tetrahydropyridine synthesis described in the next procedure.

9. Distilled product showed a proton NMR at 250 MHz in CDCl_3 as follows: δ : 0.14 (s, 9 H, SiCH_3), 1.61 (broad s, 1 H, OH), 2.37-2.46 (m, 2 H, $\text{CH}_2\text{CH}_2\text{OH}$), 3.68 (broadened t, 2 H, $J = 6.5$, CH_2OH), 5.66-5.71 (dt, 1 H, $J = 14.1$, $J = 1.2$, $\text{Me}_3\text{SiCH}=\text{CHR}$), 6.29 (overlapping dt, 1 H, $J = 14.1$, $J = 7.1$, $\text{R}_3\text{SiCH}=\text{CHR}$). Gas chromatographic analysis using a 25-m 5% methylphenylsilicone column showed that this sample was a 92:8 mixture of Z and E isomers and contained <2% of other impurities.

10. The submitters report that Z-4-(trimethylsilyl)-3-buten-1-ol of >90% isomeric purity can be obtained in ca. 60% overall yield by a more lengthy sequence involving hydroalumination-protonolysis³ of the tetrahydropyranyl (THP) ether of 4-(trimethylsilyl)-3-butyne-1-ol⁴ followed by cleavage⁵ of the THP ether with pyridinium p-toluenesulfonate in methanol. This sequence is less convenient for the tetrahydropyridine synthesis described in the next procedure, since the isomeric purity of the vinylsilane is not important for the cyclization reaction.⁶

3. Discussion

The direct silylation of 3-butyne-1-ol follows the Danheiser modification⁷ of the Westmuze-Vermeer⁸ method. The subsequent semihydrogenation is a modification⁹ of the Lindlar procedure and yields the Z-alkene isomer in >90% isomeric purity.

The following *Organic Syntheses* procedure¹⁰ illustrates one⁶ of the uses of the 4-carbon organosilane intermediates described in this preparation.

1. Department of Chemistry, University of California, Irvine, CA 92717.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(Z)-4-(Trimethylsilyl)-3-buten-1-ol: 3-Buten-1-ol, 4-(trimethylsilyl)-,

(Z)- (11); (87682-77-7)

4-(Trimethylsilyl)-3-butyne-1-ol: 3-Butyne-1-ol, 4-(trimethylsilyl)- (9);

(2117-12-6)

3-Butyne-1-ol (8,9); (927-74-2)

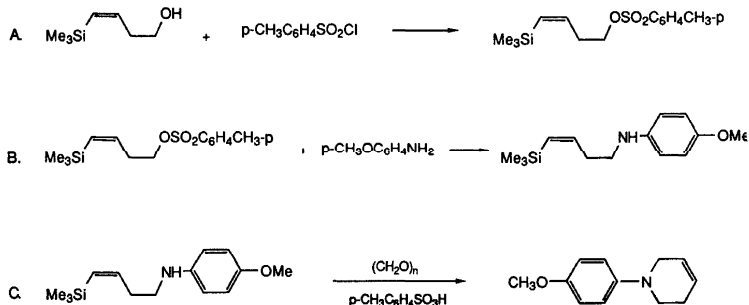
Ethylmagnesium bromide: Magnesium, bromoethyl- (9); (925-90-6)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Quinoline (8,9); (91-22-5)

REGIOSELECTIVE SYNTHESIS OF TETRAHYDROPYRIDINES:

1-(4-METHOXYPHENYL)-1,2,5,6-TETRAHYDROPYRIDINE



Submitted by Larry E. Overman, Chris J. Flann, and Thomas C. Malone.¹

Checked by Ronald C. Newbold and Andrew S. Kende.

1. Procedure

A. *Preparation of (Z)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate.* An oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and purged with dry argon or nitrogen. The flask is charged with 17.3 g (0.120 mol) of (Z)-4-(trimethylsilyl)-3-buten-1-ol (Note 1) and 290 mL of dry pyridine (Note 2). The reaction mixture is cooled to 0°C in an ice-water bath and 25.2 g (0.132 mol) of p-toluenesulfonyl chloride (Note 3) is added to the solution. When the p-toluenesulfonyl chloride is

completely dissolved, the flask containing the reaction mixture is sealed and placed in a refrigerator at -20°C for 24 hr (Note 4). The reaction mixture is then poured into a rapidly stirring mixture of 200 g of ice and 200 mL of water contained in a 2-L Erlenmeyer flask. The resulting mixture is transferred to a 2-L separatory funnel and extracted with five 200-mL portions of ether. The combined organic phases are washed with five 200-mL portions of ice-cold aqueous 6 N hydrochloric acid (Note 5) and 200 mL of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give 29.2 g (82%) of crude (Z)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate as a light yellow oil (Note 6).

B. Preparation of N-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a 250-mL addition funnel, and a gas inlet tube. The flask is flushed with argon or nitrogen and charged with 41.5 g (0.337 mol) of 4-methoxyaniline (Note 7) and then heated to 65°C . The stirring melt is degassed (Note 8), 20.2 g (67.8 mmol) of (Z)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate is added over 15 min, and the resulting solution is maintained at 65°C for 3 hr. The reaction product is allowed to cool to ca. 50°C and is then transferred to a 500-mL separatory funnel using 250 mL of chloroform. The chloroform solution is washed with two 100-mL portions of 1 M sodium hydroxide and the combined aqueous phases are extracted with 500 mL of chloroform. The combined organic phases are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue is distilled through a 17-cm Vigreux column and excess 4-methoxyaniline is collected in the first fraction, bp $80-86^{\circ}\text{C}$ (0.25 mm) (Note 9). Vacuum distillation is continued to give 10.6 g (63% yield) of

N-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine, bp 125-128°C (0.25 mm), as a pale yellow oil (Note 10).

C. *Preparation of 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine.* An oven-dried, 250-mL, two-necked round-bottomed flask is equipped with a magnetic stirring bar, reflux condenser, and an argon or nitrogen inlet. The flask is flushed with argon or nitrogen, charged with 6.62 g (26.5 mmol) of N-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine, 7.45 g (260 mmol) of paraformaldehyde (Note 11), 4.8 g (25 mmol) of p-toluenesulfonic acid monohydrate (Note 12) and 100 mL of acetonitrile (Note 13). The reaction mixture is degassed (Note 8) and heated at reflux for 1 hr (Note 14). The reaction mixture is cooled to room temperature and the excess paraformaldehyde is removed by vacuum filtration. The reaction vessel is washed with two 25-mL portions of dichloromethane and the washings are clarified by filtration. The combined organic phases are concentrated under reduced pressure using a rotary evaporator and the resulting solid residue is dissolved in dichloromethane and transferred to a 500-mL separatory funnel. The organic phase is washed with two 100-mL portions of 4 M sodium hydroxide and the aqueous washings are extracted with 50 mL of dichloromethane. The combined organic phases are then washed with 100 mL of water, dried over anhydrous potassium carbonate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue is dissolved in 9:1 hexane-ether and filtered through a 20-cm column (6-cm diameter) of silica gel. Evaporation of solvent gives 4.2 g (84% yield) of 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine as a white crystalline solid, mp 49-51°C (Notes 15, 16).

2. Notes

1. The trimethylsilyl butenol was prepared as described in the previous *Organic Syntheses* procedure.
2. Pyridine is freshly distilled from calcium hydride under an argon atmosphere.
3. p-Toluenesulfonyl chloride was purchased from Aldrich Chemical Company, Inc. and was purified by dissolving 100 g in 100 mL of chloroform, adding 1250 mL of hexane, filtering to remove insoluble impurities, and concentrating the filtrate under reduced pressure.²
4. During this time, pyridinium hydrochloride precipitates from the solution as white needles.
5. Caution must be exercised so that the ether layer does not become too warm during this extraction.
6. The sample has the following spectral characteristics: IR (neat) cm^{-1} : 1610, 1365, 1255, 1180. ^1H NMR (CDCl_3 , 250 MHz) δ : 0.13 (s, 9 H, SiCH_3), 2.49-2.58 (m, 5 H), 4.14 (apparent t, 2 H, $J = 6.9$, CH_2OR), 5.69 (d, 1 H, $J = 14.1$, $\text{R}_3\text{SiCH}=\text{CH}$), 6.17 (overlapping dt, 1 H, $J = 14.1$, $J = 7.2$, $\text{R}_3\text{SiCH}=\text{CH}$), 7.40 (apparent d, 2 H, $J = 7.8$, aryl H), 7.85 (apparent d, 2 H, $J = 8.3$, aryl H). Gas chromatographic analysis using a 25-m 5% methylphenyl-silicone column showed that this sample was >92% pure and contained several unidentified impurities.
7. 4-Methoxyaniline (p-anisidine) was purchased from Aldrich Chemical Company, Inc.
8. This is done by applying a mild vacuum to the reaction vessel and then filling the vessel with argon or nitrogen. This operation was repeated three times.

9. The condenser is not cooled and the collector tip is at times gently heated with a heat gun to prevent crystallization of 4-methoxyaniline in the distillation apparatus.

10. The product had the following spectral characteristics: IR (neat) cm^{-1} : 3390, 2950, 1608, 1246, 1040, 838; ^1H NMR (CDCl_3 , 250 MHz) δ : 0.14 (s, 9 H, SiCH_3), 2.42-2.51 (apparent q, 2 H, $J = 7$, $=\text{CHCH}_2$), 3.15 (t, 2 H, $J = 6.8$, CH_2NR), 3.76 (s, 3 H, ArOCH_3), 5.67 (d, 1 H, $J = 14.1$, $\text{R}_3\text{SiCH}=\text{CH}$), 6.32 (overlapping dt, 1 H, $J = 14.1$ and 7.3, $\text{R}_3\text{SiCH}=\text{CH}$), 6.59 (apparent d, 2 H, $J = 9.0$, aryl H), 6.76 (apparent d, 2 H, $J = 9.0$, aryl H). High resolution mass spectrum (EI, 70 eV) 249.1548 (Calcd for $\text{C}_{14}\text{H}_{23}\text{NOSi}$: 249.1549). Gas chromatographic analysis using a 25-m 5% methylphenylsilicone capillary column showed that this sample was >95% pure. Two impurities of similar retention time, presumed to be the (E)-stereoisomer and the corresponding alkane, comprise from 1-3% of the product mixture depending on the run, while a third, longer retention time impurity, the corresponding tertiary amine, comprises 2% of the product mixture.

11. Paraformaldehyde was purchased from Alpha Products, Morton/Thiokol Inc.

12. p-Toluenesulfonic acid monohydrate was purchased from Aldrich Chemical Company, Inc. and is suitable for use after storage for 24 hr in a vacuum desiccator over phosphorus pentoxide..

13. Acetonitrile was purchased from Mallinkrodt, Inc.

14. During this time paraformaldehyde can be seen forming on the inside of the reflux condenser.

15. The sample thus obtained is 94-97% pure by capillary GC analysis using a 25-m 5% methylphenylsilicone capillary column. This material gave the following elemental analysis: Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.49; H, 8.15; N, 7.31.

16. A purer sample may be obtained by vacuum sublimation at 60°C (0.3 mm). The material shows the following spectral characteristics: IR (KBr) cm^{-1} : 2831, 1514, 1249, 1210, 1190, 1035, 815; ^1H NMR (250 MHz) δ : 2.4-2.7 (m, 2 H), 3.27 (t, 2 H, $J = 5.6$), 3.58-3.65 (m, 2 H), 3.80 (s, 3 H, OCH_3), 5.7-5.9 (m, 2 H, $\text{RCH}=\text{CHR}$), 6.85-6.95 (m, 4 H, aryl H). Gas chromatographic analysis using a 25-m 5% methylphenylsilicone column showed that this material was 98% pure and was contaminated with 1.8% of the starting secondary amine and 0.3% of the corresponding tertiary acyclic amine. This material melts at 50-52°C and gave the following elemental analysis: Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.18; H, 8.00; N, 7.40. The oxalate salt melts at 134-135°C and gave the following elemental analysis: Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5$: C, 60.21; H, 6.09; N, 5.01. Found: C, 60.09; H, 6.16; N, 4.98.

3. Discussion

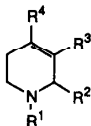
A variety of 1,2,5,6-tetrahydropyridines can be prepared by the reaction of (Z)-4-(trimethylsilyl)-3-butenamines with aldehydes.^{3,4,5} Representative examples are summarized in Table I. Cyclizations with paraformaldehyde occur readily in refluxing acetonitrile, while cyclizations with other aldehydes require higher temperatures. Tetrahydropyridines with substituents at atoms -1, -2, -3, and -4 have been regioselectively prepared in this way. In no case was any trace of a regioisomeric tetrahydropyridine detected.

The 1,2,5,6-tetrahydropyridine ring is found in several natural products and numerous pharmacologically active materials.⁵ This ring system is most commonly constructed by reduction of the corresponding pyridinium salt or from 4-piperidone precursors.^{5a} The cyclization approach reported here has the advantage of complete regiocontrol of the double-bond position. Moreover this approach is of particular value for the synthesis of 1-aryl-substituted tetrahydropyridines that are difficult to access, since they are not generally available from pyridine precursors.

Iminium ion-vinylsilane cyclizations closely related to the one described here have been used to prepare indolizidine alkaloids of the pumiliotoxin A⁶ and elaeokanine³ families, indole alkaloids,⁷ amaryllidaceae alkaloids,⁸ and the antibiotic (+)-streptazolin.⁹ The ability of the silicon substituent to control the position, and in some cases stereochemistry, of the unsaturation in the product heterocycle was a key feature of each of these syntheses.

Alternative methods for preparing 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine have not been reported.

TABLE I
PREPARATION OF SUBSTITUTED 1,2,5,6-TETRAHYDROPYRIDINES^{3,4}



R ¹	R ²	R ³	R ⁴	Cyclization Step	
				Conditions Temp., °C; Time, hr	Yield, %
C ₃ H ₇	H	H	H	80; 1.5	61
4-Methoxybenzyl	H	H	H	80; 1.5	91
Cyclohexyl	H	H	H	110; 10	54 ^a
Ph	H	H	H	80; 0.7	61
4-Methoxyphenyl	H	H	H	80; 1	84
C ₃ H ₇	C ₆ H ₁₃	H	H	120; 48	54
4-Methoxybenzyl	C ₆ H ₁₃	H	H	120; 72	64
Ph	C ₆ H ₁₃	H	H	80; 3	68
Iso-C ₄ H ₉	H	H	CH ₃	80; 2	66
Iso-C ₄ H ₉	H	H	Ph	80; 2	83
C ₃ H ₇	H	SiMe ₃	H	80; 1.2	82

^aIn this case the reaction of a cyanomethyl tertiary amine with silver trifluoroacetate in chloroform was used to initiate the cyclization instead of the reaction of an aldehyde with a secondary amine salt.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(Z)-4-(Trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate: 3-Buten-1-ol, 4-(trimethylsilyl)-, 4-methylbenzenesulfonate, (Z)- (11); (87682-62-0)

(Z)-4-(Trimethylsilyl)-3-buten-1-ol: 3-Buten-1-ol, 4-(trimethylsilyl)-, (Z)- (11); (87682-77-7)

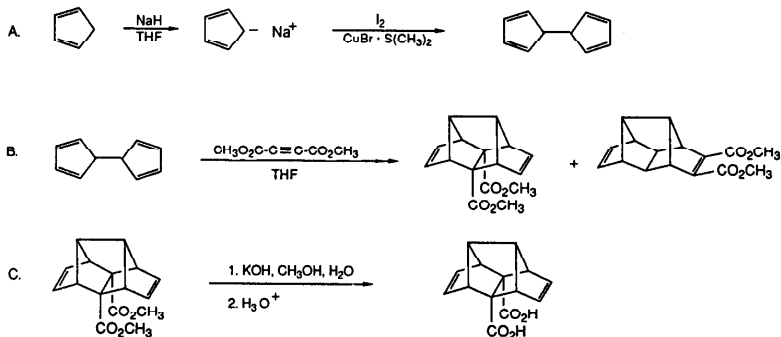
p-Toluenesulfonyl chloride (8); (Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

4-Methoxyaniline: p-Anisidine (8); Benzenamine, 4-methoxy- (9); (104-94-9)

Paraformaldehyde: Poly(oxymethylene) (8,9); (9002-81-7)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

**DOMINO DIELS-ALDER REACTION: 3,3a,3b,4,6a,7a-HEXAHYDRO-
3,4,7-METHENO-7H-CYCLOPENTA[a]PENTALENE-7,8-DICARBOXYLIC ACID
(3,4,7-Metheno-7H-cyclopenta[a]pentalene-7,8-
dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro-)**



Submitted by Richard T. Taylor,¹ Michael W. Pelter,¹ and Leo A. Paquette.²

Checked by Katsunori Nagai and Ryoji Noyori.

1. Procedure

All apparatus for Steps A and B should be dried overnight in an oven.

A. *9,10-Dihydrofulvalene*. A 5-L, three-necked, round-bottomed flask is fitted, while hot, with a Hirschberg stirrer, gas inlet, and stopper (Note 1). The assembled apparatus is flame-dried and allowed to cool to room temperature under a stream of dry, oxygen-free argon (Note 2). The stopper is

replaced with a powder funnel and, under a sweep of positive argon, 100 g (4.17 mol) of dry sodium hydride (Note 3) is added followed by 2.0 L of dry tetrahydrofuran (Note 4). The powder funnel is replaced by a 500-ml, pressure-equalizing, jacketed addition funnel which is flushed with argon, then stoppered.

The stirred sodium hydride suspension is cooled by an external ice-water bath and the jacket of the addition funnel is cooled in a dry ice-isopropyl alcohol bath. Into the addition funnel is introduced 275 g (4.16 mol) of neat, freshly distilled cyclopentadiene (Note 5). The cyclopentadiene is added rapidly, dropwise over 30-40 min to the stirred slurry (*Caution: Avoid excess foaming*) (Note 6). After the addition is complete, the cooling bath is removed and the solution is stirred for 1 hr at room temperature.

The jacketed addition funnel is removed and 1.5 g of cuprous bromide-dimethyl sulfide complex (Note 7) is added through a powder funnel. A 500-ml, pressure-equalizing addition funnel (long-tipped) is attached to the flask and flushed with argon. As the anion solution is cooled in a dry ice-isopropyl alcohol bath, a solution of 530 g (2.08 mol) of sublimed iodine in 500 mL of anhydrous tetrahydrofuran is placed in the addition funnel. This solution is added dropwise to the cooled slurry over approximately 90 min (Note 8). The solution is stirred for about 15 min at low temperature.

B. Diels-Alder reaction. A 500-ml, pressure-equalizing addition funnel containing 330 g (2.32 mol) of dimethyl acetylenedicarboxylate (Note 9) is placed in the flask and the ester is added rapidly dropwise over 10 min. The solution is stirred for 30 min, the cooling bath is removed, and stirring is maintained for 4 hr (Note 10).

The reaction solution is filtered through a Celite pad (approximately 5 cm thick on a 32-cm Büchner funnel), and the solid is washed repeatedly with tetrahydrofuran (1.5 L). The combined filtrates are concentrated under reduced pressure at a temperature not above 30°C. To the concentrate is added 1.5 L of ether. The solution is stirred for 15 min, again filtered through Celite, and concentrated at 30°C (Note 11).

C. Hydrolysis. Into a three-necked, 5-L, round-bottomed flask equipped with a mechanical stirrer, thermometer, and 500-mL addition funnel with gas inlet is placed the above concentrate and 2 L of methanol. The solution is cooled to -5° to 0°C by means of an ice-salt bath. A precooled (0°C) solution containing 220 g of 87.5% potassium hydroxide in 400 mL of water is added dropwise at such a rate as to keep the reaction temperature below 10°C. The reaction mixture is stirred for an additional 2 hr at 0°C and for 1 hr at room temperature prior to the addition of 100 mL of glacial acetic acid. Solid sodium carbonate is added to bring the pH to 8 and the solution is filtered through Celite. Concentration of the filtrate at 35°C and reduced pressure affords about 1 L of a dark liquid. The liquid is diluted with 2 L of water and extracted with petroleum ether (6 x 600 mL). The combined extracts are washed with aqueous sodium thiosulfate solution (800 mL) and dried (magnesium sulfate). Concentration at 30°C affords a clear red liquid (occasionally a yellow solid) which is almost pure internal diester (Note 12).

The diester is dissolved in 130 mL of methanol, placed in a 1-L, one-necked flask equipped with a magnetic stirrer bar and reflux condenser, and treated with a solution containing 35 g of potassium hydroxide in 130 mL of water. The mixture is stirred at reflux temperature for 1 hr. Methanol is removed under reduced pressure and 250 mL of water is added. Heating is continued for another 5 hr. After the solution is cooled, 5 g of activated

charcoal is added and the mixture is stirred for 8 hr at room temperature. Filtration through Celite is followed by cooling of the stirred filtrate in an ice bath with acidification to pH 1 (dropwise addition of concentrated hydrochloric acid). The tan solid is isolated by filtration and dried under vacuum at room temperature. On the average, the yield is 52-55 g (10-11%) but can vary from 42-68 g (8-13% yield) (Note 13).

2. Notes

1. A paste made from a 1:1 mixture of mineral oil and silicone grease is used to lubricate the stirrer.
2. Prepurified argon (Linde) can be used with no further treatment.
3. Dry sodium hydride is available from Aldrich Chemical Company, Inc., as a fine powder. In multiple runs, it is most convenient to weigh the bulk reagent into 100-g (one reaction) lots. Extreme care should be used in handling this moisture-sensitive, flammable solid.
4. Tetrahydrofuran is distilled from calcium hydride and then from sodium-benzophenone immediately prior to use.
5. This amount of cyclopentadiene can be prepared in 2-3 hr using any of a variety of procedures.³⁻⁵
6. The checkers transferred cyclopentadiene by using a stainless steel cannula from a cooled (dry ice-methanol), 500-mL, round-bottomed flask to the reaction vessel.
7. The complex was purchased from Aldrich Chemical Company, Inc.
8. A bright emerald green color (usually) develops as the addition proceeds. If the iodine is impure, a brown color develops with no decrease in yield.

9. While dimethyl acetylenedicarboxylate is available commercially, it is easily prepared by the procedure of Huntress, Lesslie, and Bornstein.⁶ Care should be taken with this compound as it is a severe lachrymator and vesicant.

10. A tan to white precipitate of sodium iodide forms and a gentle exotherm is observed.

11. This concentrate (a dark red oil) may be stored in a refrigerator if time does not permit further work.

12. While the Diels-Alder reaction affords a wide variety of products, all of the esters formed hydrolyze faster than the desired internal adduct. The above hydrolysis removes all byproducts through base extraction. The internal diester has spectral properties as follows: ¹H NMR (CDCl₃) δ: 2.50 (tt, 2 H, J = 2.0, 4.3), 3.30 (dd, 4 H, J = 2.0, 4.3), 3.59 (s, 6 H), 6.07 (t, 4 H, J = 2.0); ¹³C NMR (CDCl₃) δ: 51.5, 58.8, 64.4, 69.5, 132.7, 172.7.

13. Spectral properties of the diacid are as follows: ¹H NMR (DMSO-d₆) δ: 2.36 (tt, 2 H, J = 1.5, 4.1), 3.21 (dd, 4 H, J = 1.5, 4.1), 5.95 (t, 4 H, J = 1.7).

3. Discussion

The present procedure is a modification of the method previously reported.⁷ While the overall yield is similar, the method described here is simpler in that it avoids a cumbersome transfer of the sodium cyclopentadienide solution.

The first step leading to 9,10-dihydrofulvalene is adapted from the earlier work of Matzner.⁸ The utility of this thermally labile hydrocarbon ranges from its ability to engage in multiple [4+2] cycloadditions^{7,9} to its capacity for bonding to a pair of metal atoms.¹⁰

The product diacid has served as starting material for the synthesis of tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodeca-2,7-diene-5,12-dione,¹¹ C₁₆-hexaquinacene,¹² (C₅)-C₁₇-heptaquinane derivatives,¹³ the parent dodecahedrane molecule,¹⁴ and a number of substituted dodecahedranes.¹⁵

1. Department of Chemistry, Miami University, Oxford, OH 45056.
2. Department of Chemistry, The Ohio State University, Columbus, OH 43210.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,3a,3b,4,6a,7a-Hexahydro-3,4,7-metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid: 3,4,7-Metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro- (10); (61206-25-5)

9,10-Dihydrofulvalene: Bi-2,4-cyclopentadien-1-yl (8,9); (21423-86-9)

Cyclopentadiene: 1,3-Cyclopentadiene (8,9); (542-92-7)

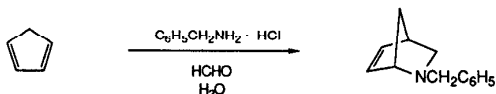
Dimethyl acetylenedicarboxylate: Acetylenedicarboxylic acid, dimethyl ester (8); 2-Butynedioic acid, dimethyl ester (9); (762-42-5)

Dimethyl 3,3a,3b,4,6a,7a-hexahydro-3,4,7-metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylate: 3,4,7-Metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro-, dimethyl ester (9); (53282-97-6)

IMMONIUM ION-BASED DIELS-ALDER REACTIONS:

N-BENZYL-2-AZANORBORNENE

(2-Azabicyclo[2.2.1]hept-5-ene, 2-(phenylmethyl)-)



Submitted by Paul A. Grieco and Scott D. Larsen.¹

Checked by V. Ramamurthy and Bruce E. Smart.

1. Procedure

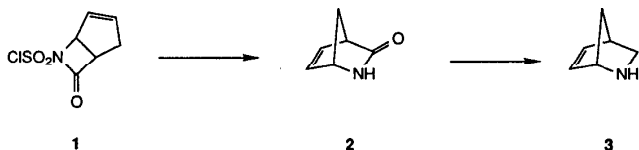
A 100-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 24 mL of de-ionized water and 8.6 g (60.0 mmol) of benzylamine hydrochloride (Note 1). To the above homogeneous solution is added 6.3 mL (84 mmol) of 37% aqueous formaldehyde solution (Note 2) followed by 9.9 mL (120 mmol) of freshly prepared cyclopentadiene (Note 3). The flask is stoppered tightly (Note 4) and stirred vigorously at ambient temperature. After 4 hr, the reaction mixture is poured into 50 mL of water and washed with ether-hexane, 1:1 (2 x 40 mL). The aqueous phase is made basic by the addition of 4.0 g of solid potassium hydroxide and extracted with ether (3 x 60 mL). The combined ether extracts are dried over anhydrous magnesium sulfate and filtered. The solvent is removed under reduced pressure (15-20 mm) to give 11.2 g (100%) of N-benzyl-2-azanorbornene as a very pale yellow oil (Note 5). The crude product is distilled at 80-85°C (0.05 mm) (Note 6) through a short path apparatus to provide 10.1-10.2 g (91-92%) of pure product (Note 7) as a colorless oil (Note 8).

2. Notes

1. Benzylamine hydrochloride is commercially available from Aldrich Chemical Company, Inc.
2. Aqueous formaldehyde solution (37%) is commercially available from Mallinckrodt Inc.
3. Cyclopentadiene is prepared by heating commercial dicyclopentadiene (available from Aldrich Chemical Company, Inc.) at 160°C in a distillation apparatus. Cyclopentadiene distills smoothly at 39-45°C.²
4. The heterogeneous reaction mixture is stoppered tightly to avoid loss of cyclopentadiene.
5. This crude material is essentially pure product contaminated by trace amounts of ether. N-Benzyl-2-azanorbornene has the following spectrum: ¹H NMR (300 MHz, CDCl₃) δ: 1.42 (dm, 1 H, J = 8), 1.52 (dd, 1 H, J = 2, 8.5), 1.64 (dm, 1 H, J = 8), 2.94 (bs, 1 H), 3.18 (dd, 2 H, J = 3, 8.5), 3.34, 3.58 (AB, 2 H, J = 13), 3.83 (m, 1 H), 6.09 (dd, 1 H, J = 2, 6), 6.38 (ddd, 1 H, J = 2, 3, 6), 7.2-7.4 (m, 5 H).
6. Attempted distillation at 15-20 mm resulted in extensive decomposition.
7. The submitters obtained 10.8 g (97%) of analytically pure product, bp 80-85°C (0.05 mm). Anal. Calcd for C₁₃H₁₅N: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.68; H, 8.36; N, 7.59.
8. Upon prolonged standing in air at room temperature discoloration of the product accompanied by slow evolution of cyclopentadiene takes place.

3. Discussion

Simple unactivated immonium salts generated in situ from formaldehyde and primary alkyl amines undergo a facile aza Diels-Alder reaction with cyclopentadiene at ambient temperature³ to afford novel N-alkylated 2-azanorbornenes. The procedure described above is general and can be applied to a number of primary alkyl amines. Yields of N-alkyl substituted 2-azanorbornenes are good to excellent. Use of ammonium chloride and formaldehyde in the above reaction produces 2-azanorbornene in modest (40-50%) yield. 2-Azanorbornene (3) has been previously prepared⁴ by reaction of cyclopentadiene with chlorosulfonyl isocyanate which provides a single N-chlorosulfonyl β -lactam (1). Exposure of 1 to an aqueous solution of sodium sulfite gives rise (25-30%) to 2-azanorbornen-3-one (2) which upon reduction with lithium aluminum hydride affords (ca. 80%) 2-azanorbornene (3).



1. Department of Chemistry, Indiana University, Bloomington, IN 47405.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

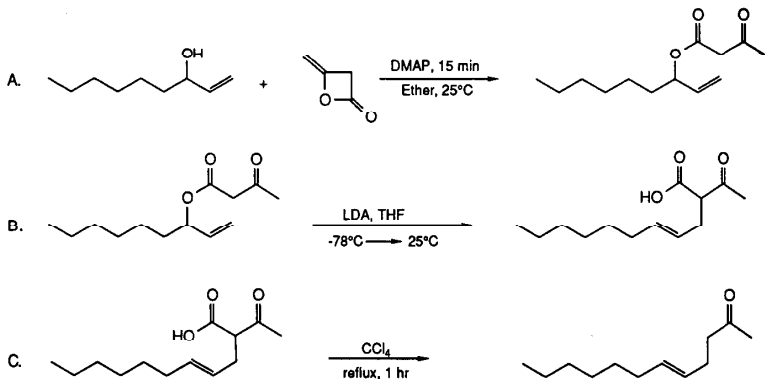
Benzylamine hydrochloride (8); Benzenemethanamine, hydrochloride (9);
(3287-99-8)

Formaldehyde (8,9); (50-00-0)

Cyclopentadiene: 1,3-Cyclopentadiene (8,9); (542-92-7)

THE CARROLL REARRANGEMENT: 5-DODECEN-2-ONE

(5-Dodecen-2-one, (E)-)



Submitted by Stephen R. Wilson and Corinne E. Augelli.¹

Checked by T. R. Vedananda and James D. White.

1. Procedure

A. *(1-Ethenyl)heptyl 3-ketobutanoate*. 3-Hydroxy-1-nonene (Note 1, 7.5 g 0.053 mol) is stirred in 250 ml of anhydrous ether (Note 2) in a 500-mL, three-necked, round-bottomed flask, fitted with a thermometer, nitrogen/mineral oil bubbler, Teflon-covered magnetic stirring bar, and a rubber septum. A constant flow of nitrogen is maintained throughout the reaction. To this clear homogeneous solution, diketene (Note 3, 5.04 g, 0.060 mol) is added in one portion by syringe, followed by 4-dimethylaminopyridine

(DMAP) (0.591 g, 0.0049 mol, Note 4). A slightly exothermic reaction (to 32°C) is observed. After 15 min, the reaction is complete (Note 5). The reaction mixture is quenched with 100 mL of 0.1% sodium hydroxide solution and 100 mL of anhydrous ether. The layers are separated and the organic phase is washed once with 50 mL of 0.1% sodium hydroxide solution and once with brine. Drying over magnesium sulfate and concentration under reduced pressure affords 11.3 g (0.05 mol, 94%) of a pale yellow oil. The β -keto ester is of high purity, as shown by TLC, GLC, and spectral analyses (Note 6); however, distillation (bp 113-114°C/1.4 mm) leads to a colorless oil.

B. 3-Carboxy-5-dodecen-2-one. A solution of lithium diisopropylamide (LDA, Note 7) in 150 mL of tetrahydrofuran (Note 8) is prepared from 0.199 mol (20.12 g) of diisopropylamine (Note 9) and 0.181 mol of butyllithium (Notes 10,11). The solution is cooled to -78°C (acetone/dry ice) and a solution of 10.0 g (0.044 mol) of (1-ethenyl)heptyl 3-ketobutanoate in 50 mL of tetrahydrofuran (Note 8) is added via a 125-mL, pressure-equalizing dropping funnel at -78°C over a 15-min period. After the addition is complete, the reaction mixture is stirred at -78°C for 45 min and is then allowed to warm gradually to room temperature. When the reaction mixture finally reaches 25°C (about 2 hr), it has a deep red color. After the mixture is stirred for 18 hr at room temperature, the reaction is complete (Note 12). To this mixture, 100 mL of water and 100 mL of pentane are added in portions with stirring, maintaining the temperature below 25°C with an ice bath. As the deep red reaction mixture is quenched, an orange heterogeneous mixture results. The layers are separated and the pentane layer is extracted two times with 50 mL of 0.1% sodium hydroxide solution (Note 13). All aqueous layers are combined in an 800-mL beaker equipped with a Teflon-covered magnetic stirring bar. A 100-mL aliquot of pentane is added to this aqueous mixture which is stirred

vigorously, and then 100 mL of 10% hydrochloric acid solution is added in 10-mL portions until pH 2 is reached (Note 14). The heterogeneous solution is poured into a 1-L separatory funnel and the layers are quickly separated. The aqueous layer is extracted three times more, each time with 50 mL of pentane. The combined organic layers (ca. 250-300 mL) are dried (MgSO_4) and evaporated at reduced pressure without heating to give 9.6 g (0.04 mol, 97%) of a red-orange oil. This carboxylic acid is of high purity as shown by TLC and spectral analyses (Note 15).

C. *5-Dodecen-8-one*. The 3-carboxy-5-dodecen-2-one (9.0 g, 0.040 mol) is stirred in 150 mL of carbon tetrachloride (Note 16) in a 500-mL, three-necked, round-bottomed flask which is fitted with a reflux condenser, thermometer, Teflon-covered magnetic stirrer, and a ground-glass stopper. After the orange-yellow solution is heated at reflux for 1 hr, TLC analysis shows the reaction to be complete (Note 17). The reaction mixture is concentrated under reduced pressure with warming to afford 7.1 g (0.039 mol, 98%) of a red-orange oil. The product is sufficiently pure for most purposes. It may be purified by vacuum distillation at 105-107°C/2.7 mm (5.2 g, 0.03 mol, 71%) which yields a pale yellow oil (Note 18).

2. Notes

1. 3-Hydroxy-1-nonene was prepared by the following procedure: 0.219 mol (25.0 g) of heptaldehyde (Eastman Kodak Co.), distilled prior to use, was stirred in 450 mL of anhydrous ether (Note 2) under a nitrogen atmosphere. The solution was cooled to 0°C with an ice bath and 0.260 mol (260.4 mL) of vinylmagnesium bromide (1.0 M solution in tetrahydrofuran, Aldrich Chemical Company, Inc., 1.2 equiv) was then added dropwise over a 0.5-hr period. The

reaction mixture was allowed to warm gradually to room temperature and was stirred for 0.5 hr. The reaction mixture was added, in portions with stirring, to 400 mL of a saturated ammonium chloride solution, maintaining the temperature below 25°C with an ice bath. This quenched reaction mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted two times, each time with 200 mL of ether. The combined organic layers were extracted with 200 mL of brine, dried (MgSO_4) and concentrated under reduced pressure with warming to afford a yellow oil in quantitative yield. The allylic alcohol was distilled (bp 185°C/760 mm, 22.5 g 0.158 mol, 73%) before use. Silica gel TLC showed one spot: $R_f = 0.34$ (20% ethyl acetate/ligroin). GLC: Retention time, 4.56 min; Program: 40°C/1 min; 20°C/1 min to 320°C; 2% OV-101, 0.2% Carbowax on Chromosorb. This program and column were used throughout the entire sequence of reactions. IR (neat) cm^{-1} : 3610 (OH); 3000 (C-H, alkenes); 1650 (C=C); 1000 (C-O). Mass spectrum: m/e 57 (100% M^+ - $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 85 (7.7% M^+ - $\text{CHOHCH}=\text{CH}_2$), 113 (2.5% M^+ - CH_2CH_3). ^1H NMR (CDCl_3) δ : 0.91 (t, 1 H, $J = 6.9$); 1.54-1.31 (m, 11 H); 4.12 (q, 1 H, $J = 6.3$); 5.27-5.11 (m, 1 H); 5.95-5.84 (m, 1 H). ^{13}C NMR (CDCl_3) δ : 14.0, 22.6, 25.4, 29.3, 31.9, 37.1, 72.9, 114.0, 141.5.

2. Anhydrous ether (Fisher Scientific Company) was used without further drying.

3. Diketene (Aldrich Chemical Company, Inc.) was distilled immediately prior to use.

4. 4-Dimethylaminopyridine (DMAP) was purchased from Aldrich Chemical Company, Inc. A catalytic amount of 4-dimethylaminopyridine is necessary for this reaction to proceed.

5. Reaction progress can be monitored by GLC analysis of the disappearance of diketene.

6. Silica gel TLC shows one spot at $R_f = 0.45$ (20% ethyl acetate/ligroin); GLC shows >95% purity of the β -keto ester. The β -keto ester undergoes partial cleavage to the corresponding allylic alcohol under these GLC conditions: Retention time, 7.8 ((1-ethenyl)heptanyl 3-ketobutanoate); retention time, 4.88 (3-hydroxy-1-nonene). Mass spectrum for the β -keto ester: m/e 43 (100% $M^+ - COCH_3$), 85 (46.5% $(CH_2)_5CH_3$), 141 (13.3% $M^+ - COCH_2COCH_3$). Mass spectrum for allylic alcohol: m/e 57 (100% $M^+ - CH_2(CH_2)_4CH_3$), 85 (8.7% $M^+ - CHOHCH=CH_2$), 113 (2.8% $M^+ - CH_2CH_3$). IR (neat) cm^{-1} : 3000 (C-H, alkenes); 1725 (C=O); 1650 (C=C). 1H NMR ($CDCl_3$) δ : 0.89 (t, 3 H); 1.30-1.64 (m, 10 H); 2.3 (s, 3 H), 3.47 (s, 2 H); 5.19-5.31 (m, 3 H); 5.72-5.84 (m, 1 H). Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.8. Found: C, 69.25; H, 10.06.

7. Lithium diisopropylamide (LDA) was prepared by the method described in *Org. Synth.* 1985, 64, 68-72.

8. Tetrahydrofuran was distilled from lithium aluminum hydride immediately prior to use.

9. Diisopropylamine, purchased from Aldrich Chemical Company, Inc., was distilled immediately prior to use.

10. Butyllithium, 2.5 M solution, in hexanes was purchased from Aldrich Chemical Company, Inc. Butyllithium was titrated with diphenylacetic acid² before each use.

11. An amount of 4.1 equiv of lithium diisopropylamide (LDA) is absolutely necessary for this reaction to go to completion. An equilibrium exists between the formation of the second anion of the β -keto ester and the formation of lithium diisopropylamide from diisopropylamine.

12. Reaction progress can be followed most accurately by silica gel TLC and GLC analysis. In TLC analysis, one sees the disappearance of (1-ethenyl)-

heptanyl 3-ketobutanoate, $R_f = 0.45$ (20% ethyl acetate/ligroin) and the appearance of baseline material which is indicative of the corresponding carboxylic acid salt. In GLC analysis, an aliquot (3 drops of reaction mixture, 3 drops of ether, 3 drops of 10% hydrochloric acid) will show complete disappearance of peaks at $R_t = 7.44$ and 4.56 (which correspond to (1-ethenyl)heptanyl 3-ketobutanoate and cleavage of this β -keto ester under GLC conditions to the 3-hydroxy-1-nonene, respectively) and appearance of a peak at $R_t = 7.04$ which corresponds to 5-dodecen-2-one. The 3-carboxy-5-dodecen-2-one decarboxylates upon injection yielding the GLC spectrum of the ultimate product.

13. Sodium hydroxide (0.1%) is used to extract all of the carboxylate from the ether layer in the form of the sodium salt.

14. A slight exotherm was noted from 25°C to 32°C. Acidification is necessary to extract all of the desired carboxylate from the aqueous layer into the organic layer.

15. Silica gel TLC shows one major spot at the baseline (20% ethyl acetate/ligroin) with a very slight impurity (<5%) at $R_f = 0.47$. Mass spectrum of 5-dodecen-2-one: m/e 43 (100% COCH_3), 97 (6.1% M^+ - $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 125 (1.7% M^+ - CH_2COCH_3). IR (neat) cm^{-1} : 3000 (COOH); 1725 (COOH , RCOR). ^1H NMR (CDCl_3) δ : 0.90 (t, 3 H, $J = 6.3$); 1.28 (m, 8 H); 2.00 (m, 2 H); 2.31 (s, 3 H); 2.60 (t, 2 H, $J = 6.9$); 3.48-3.59 (m, 1 H); 5.27-5.44 (m, 1 H, trans $J = 15.3$); 5.49-5.61 (m, 1 H, trans $J = 15.3$).

16. Carbon tetrachloride was used as purchased from Fisher Scientific Company.

17. Reaction progress was followed most accurately by TLC analysis. The disappearance of the baseline material (i.e., 3-carboxy-5-dodecen-2-one) and appearance of the desired ketone at $R_f = 0.33$ (10% ethyl acetate/ligroin) indicates the completeness of the reaction.

18. Silica gel TLC shows one spot at $R_f = 0.33$ (10% ethyl acetate/ligroin). GLC shows >95% purity; one peak at $R_t = 7.04$. Mass spectrum: m/e 43 (100% COCH_3), 97 (6.3% $\text{M}^+ - \text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 125 (2.0% $\text{M}^+ - \text{CH}_2\text{COCH}_3$). IR (neat) cm^{-1} : 1700 ($\text{R}'\text{COR}$). ^1H NMR (CDCl_3) δ : 0.90 (t, 3 H, $J = 6.5$); 1.28 (m, 8 H); 1.98 (q, 2 H, $J = 6.3$); 2.16 (s, 3 H); 2.28 (q, 2 H, $J = 6.6$); 2.51 (t, 2 H, $J = 7.4$); 5.34-5.51 (m, 2 H). ^{13}C NMR (CDCl_3) δ : 14.0, 22.6, 26.9, 28.8, 29.5, 29.8, 31.7, 32.5, 43.6, 128.2, 131.5, 207.9. Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}$: C, 79.06; H, 12.17. Found: C, 78.79; H, 12.10.

3. Discussion

The Carroll rearrangement,^{3,4} an old and well-established thermal rearrangement, involves the rearrangement of allylic esters to β -keto acids followed by decarboxylation to provide γ,δ -unsaturated methyl ketones. Even though the Carroll rearrangement is a versatile complement to the Claisen rearrangement,⁵ it is not of widespread use. This may be due to: (a) the lack of a convenient, high yield method for the formation of β -keto esters and (b) the harsh conditions required to effect rearrangement.⁶ Often, procedures involve direct conversion of allylic alcohols to the rearranged and decarboxylated products in one step and low yield.

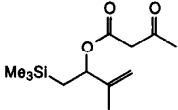
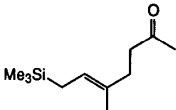
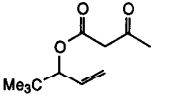
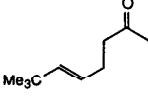
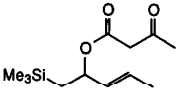
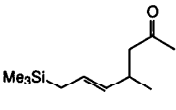
The method of preparation of 5-dodecen-2-one presented here is a version of the literature procedure published earlier.⁷ It offers several advantages over existing methodology: (1) The ester enolate modification of the Carroll rearrangement provides the allylic acetoacetates via a mild, fast, and high yield synthesis. This procedure represents a significant improvement over other routes.⁸ (2) Dianions of the allylic acetoacetates rearrange at room temperature and the resulting β -keto acids can be readily isolated. Isolation

of the acetoacetic acids adds to the versatility of the synthesis of γ,δ -unsaturated methyl ketones and makes purification much more simple than the pyrolysis method. (3) Finally, the general pyrolysis procedure, although one step, leads to side products and low yields (typically 10-40%). For example, pyrolysis of (1-ethenyl)heptanyl 3-ketobutanoate⁴ gives two major products, 5-dodecen-2-one and 3-hydroxy-1-nonene, whereas the method of preparation described here yields only the desired γ,δ -unsaturated methyl ketone.

The Table contains representative examples of the method of preparation described here.

1. Department of Chemistry, New York University, Washington Square, New York, NY 10003.
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4. Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.
5. Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
6. Rearrangement is normally carried out at temperatures of 130-220°C by heating the β -keto ester neat or in a high boiling solvent (xylene, diphenyl ether), usually in situ after preparation of the β -keto ester.
7. Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.
8. Acetoacetate formation has previously been carried out by using the following. (a) Et₃N: Kato, T.; Chiba, T. *Chem. Pharm. Bull.* **1975**, *23*, 2263; (b) NaOR: See ref. 4; (c) p-TsOH: Boese, A. B., Jr. *Ind. Eng. Chem.* **1940**, *52*, 16.

TABLE
PREPARATION OF γ,δ -UNSATURATED METHYL KETONES

SUBSTRATE	PRODUCT	YIELD	REF.
		40%	7
		80%	7
		84%	7

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

5-Dodecen-2-one: 5-Dodecen-2-one, (E)- (11); (81953-05-1).

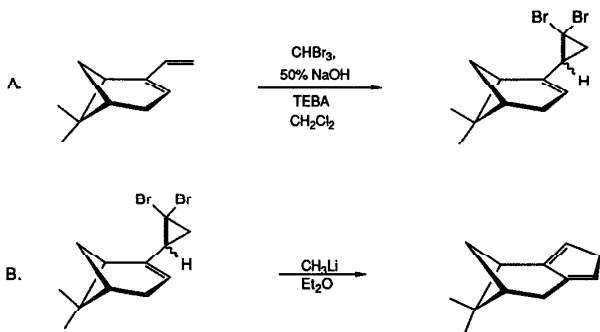
3-Hydroxy-1-nonene: 1-Nonen-3-ol (8,9); (21964-44-3)

Diketene: 2-Oxetanone, 4-methylene- (8,9); (674-82-8)

4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

CYCLOPENTADIENE ANNULATION VIA THE SKATTEBØL REARRANGEMENT:

(1R)-9,9-DIMETHYLTRICYCLO[6.1.1.0^{2,6}]DECA-2,5-DIENE



Submitted by Leo A. Paquette and Mark L. McLaughlin.¹

Checked by Nanine Van Draanen and Clayton H. Heathcock.

1. Procedure

A. *Dibromocyclopropane addition to (1R)-nopadiene.* A 250-mL, three-necked flask is equipped with a mechanical stirrer, nitrogen inlet, and serum cap. The flask is charged with 26.2 mL (0.30 mol) of bromoform (Note 1), 29.6 g (0.20 mol) of (1R)-nopadiene (Notes 2 and 3), 1.0 g (4.4 mmol) of benzyltriethylammonium chloride (TEBA), 0.8 mL of ethanol, and 20 mL of dichloromethane (Note 4). The suspension is stirred and cooled in an ice bath while 100 mL of 50% sodium hydroxide solution is added over 10 min from a dropping funnel. The reaction mixture is stirred at room temperature for 24 hr and poured into 250 mL of water. The lower layer is separated and the

aqueous phase is extracted with three 25-mL portions of dichloromethane. The combined organic layers are washed with three 100-mL portions of water, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown-black oil. The oil is dissolved in an equal volume of hexane and filtered through a 2-in bed of silica with hexane (1.5 L) as eluant. The solvent is evaporated and the orange oil is distilled in an apparatus protected from light (Note 5) at 85-95°C and 0.08 mm. The yellow distillate is redistilled through a 4-in Vigreux column to give 32.0-33.6 g (50-53%) of the diastereomeric dibromocyclopropanes (Note 6).

B. (1R)-9,9-Dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-diene. A flame-dried, 3-L flask is equipped with a large magnetic stirring bar and serum cap and charged with 17.6 g (55.0 mmol) of the dibromide. A total of 2 L of anhydrous ether (Note 7) is transferred into the flask via cannula. The stirred solution is cooled in an ice bath and 147 mL of 1.5 M methyllithium in ether (220 mmol) is introduced via a second cannula (Note 8). The ice bath is removed and stirring is maintained for 10 hr before the solution is transferred by cannula into 1 L of ice-cold water. The ether layer is separated and the aqueous phase is extracted with two 200-mL portions of ether. The combined ethereal solutions are dried and concentrated (Note 9). The residual yellow oil is immediately diluted with an equal volume of hexane and passed through a short column of neutral alumina (Note 10). The solvent is carefully removed and the yellow oil is subjected to bulb-to-bulb distillation at 90°C and 5 mm (Note 11). The yield of colorless hydrocarbon is 6.9-7.1 g (78-80%) (Notes 12 and 13).

2. Notes

1. The submitters used a purified grade of bromoform purchased from the Fisher Chemical Company.

2. The (1R)-nopadiene is prepared from commercially available (Aldrich Chemical Company, Inc.) (1R)-(-)-nopol (Note 3) according to the following procedure.² A 1000-mL, three-necked flask is equipped with a mechanical stirrer, internal thermometer and nitrogen inlet. The flask is charged with 125 g (0.752 mol) of (1R)-(-)-nopol and 500 mL of pyridine. Stirring is begun and the solution is cooled to -10°C in an ice-salt bath under nitrogen. p-Toluenesulfonyl chloride (175 g, 0.918 mol) is added in one portion under an inert atmosphere via Gooch tubing (the checkers used a powder funnel for the addition). The temperature rises to 40°C for 15-20 min, but returns to 5°C where it is maintained for 2 hr. Twenty 1-mL portions of water are next introduced at such a rate that the temperature does not exceed 5°C. The reaction mixture is poured into 1 L of ether and extracted with ice-cold 5 M sulfuric acid until the aqueous layer remains acidic, then with saturated CuSO_4 solution until the aqueous layer remains blue. The ethereal phase is washed with two 200-mL portions each of water and 5% sodium bicarbonate solution prior to drying over magnesium sulfate and solvent evaporation. A solid residue is obtained. If this material is dark, it may be dissolved in hexane and filtered through a pad of Celite to remove the black impurity. The tosylate is recrystallized by dissolving it in 500 mL of hot hexane and cooling to -78°C. Six such recrystallizations give material with mp 51.0-51.8°C and $[\alpha]_D^{25}$ -25.6° ($\text{C}_2\text{H}_5\text{OH}$, c 0.03). The yield is 65-72%.

A 2000-mL, three-necked flask is equipped with a mechanical stirrer, internal thermometer, and nitrogen inlet. The flask is charged with 200 g (0.624 mol) of (1R)-nonyl tosylate and 1000 mL of dimethyl sulfoxide which has been freshly distilled from calcium hydride at 40 mm. The stirring solution is cooled briefly in a cold water bath and 69.0 g (0.615 mol) of freshly sublimed potassium tert-butoxide is added rapidly while nitrogen is flowing above the solution (the checkers used potassium tert-butoxide from a freshly-opened bottle). (The base must be the limiting reagent to offset isomerization of the product diene). The temperature rises to approximately 45°C and a brown color develops. As the reaction proceeds, the color dissipates to a light yellow. After the initial exotherm subsides, the mixture is heated at 75°C for 10 hr, cooled to room temperature, and diluted with 800 mL of hexane. The lower layer, mostly dimethyl sulfoxide, is diluted with 1 L of water and extracted with two 100-mL portions of hexane. The combined hexane layers are washed with water (5 x 200 mL), dried over magnesium sulfate, and rotary evaporated at 40 mm and 25°C to leave a yellow oil. Distillation through a 5-in Vigreux column gives 69.4-74.0 g (75-80%) of (1R)-nopadiene as a clear colorless oil, bp 78-79°C/25 mm.

3. This compound is mislabelled and misdrawn in the 1987 and 1988 Aldrich catalogs as the S-enantiomer.

4. These phase-transfer conditions are adapted from experimental procedures described earlier.^{3,4}

5. The dibromocyclopropane is light-sensitive when hot. Exposure to light during distillation produces colored impurities that cause autocatalytic decomposition of the product when subsequently stored in the cold.

6. Both distillations must be performed with a pot temperature below 150°C in order to avoid thermal decomposition. ^1H NMR indicates the product to be a 4:1 mixture of diastereomers. All available evidence denotes that both are transformed efficiently into the cyclopentadiene.

7. The ether was freshly distilled from sodium benzophenone ketyl. The checkers used anhydrous ether from a freshly-opened can.

8. The methyllithium was purchased from the Aldrich Chemical Company, Inc., and contains lithium bromide.

9. Solvent evaporation was accomplished at 40 mm and 25°C in order to counter product volatility.

10. The checkers used a 1" x 1" plug of alumina. The experience of the submitters has been that the use of silica gel at this point causes some decomposition.

11. The checkers found foaming to be a serious problem in this distillation. The problem is ameliorated by use of a 50-mL or larger distillation flask.

12. Purified diene polymerizes within 24 hr if stored neat. Its lifetime can be indefinitely prolonged by storage as a 10% by weight solution in hexane under an argon atmosphere.

13. The product exhibits $[\alpha]_D^{24} -21.9^\circ$ ($\text{C}_2\text{H}_5\text{OH}$, c 1.8) and the following ^1H NMR spectrum at 300 MHz in CDCl_3 solution δ : 0.72 (s, 3 H), 1.24 (m, 1 H), 1.33 (s, 3 H), 1.60 (s, 1 H), 2.11 (m, 1 H), 2.60 (m, 1 H), 2.70 (m, 2 H), 2.99 (s, 2 H), 5.77 (s, 1 H), 5.99 (s, 1 H).

3. Discussion

Experience has shown^{5,6} that cyclopentadiene annulation of 2,3-dimethylenebicyclo[2.2.2]octanes can be efficiently realized by means of the Skattebøl procedure.⁷ However, the added strain in 2,3-dimethylenenorbornanes reroutes the rearrangement instead into vinylallene formation.⁴ This phenomenon has been attributed to an inability on the part of the torsionally-constrained empty carbene p orbital to interact with the flanking double bond.⁸ This structural inhibition is entirely alleviated by positioning the cyclopropyl carbene completely external to the norbornene ring as in the present example. The heightened conformational maneuverability of the carbenoid center is conducive to exclusive cyclopentadiene ring formation.

(1R)-9,9-Dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-diene is a chiral, optically active homolog of isodicyclopentadiene, a molecule that has been extensively studied with regard to π -facial selectivity in cycloaddition reactions.⁹ The response of the title compound to similar dienophiles has been described¹⁰ and its complexation to various transition metals reported.^{10,11} The steric contributions of the gem-dimethyl substituents relegate bonding to the opposite surface of the cyclopentadiene ring.

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Appendix

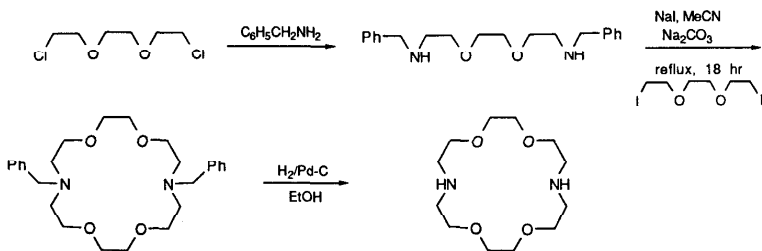
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(1R)-Nopadiene: 2-Norpinene, 6,6-dimethyl-2-vinyl-, (+) (8);
 Bicyclo[3.1.1]hept-2-ene, 2-ethenyl-6,6-dimethyl-, (1R)- (9); (30293-06-2)
 (1R)-(-)-Nopol: Bicyclo[3.1.1]hept-2-ene-2-ethanol, 6,6-dimethyl-,
 (1R)- (9); (35836-73-8)

4,13-DIAZA-18-CROWN-6

(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane)



Submitted by Vincent J. Gatto, Steven R. Miller, and George W. Gokel.¹

Checked by P. C. Prabhakaran and James D. White.

1. Procedure

A. *1,10-Dibenzyl-4,7-dioxo-1,10-diazadecane*. A solution of benzylamine (172 g, 1.6 mol) (Note 1) and 1,2-bis(2-chloroethoxy)ethane (10.7 g, 0.1 mol) (Note 2) is stirred and heated at 120°C for 28 hr. The reaction is cooled to room temperature, sodium hydroxide pellets (8.0 g, 0.2 mol) are added, and the mixture is heated at 120°C, with stirring, for 1 hr. The reaction is cooled and excess benzylamine is removed by vacuum distillation (Note 3) using a water aspirator (Note 4). The resulting oil is dissolved in chloroform (100 mL), filtered, and washed with water (50 mL) to remove salts. The organic phase is dried (Na₂SO₄) and concentrated under reduced pressure. Bulb-to-bulb distillation using a Kugelrohr apparatus (175-177°C, 0.2 mm) gives 27.9-31.2 g

(85-95%) of 1,10-dibenzyl-4,7-dioxo-1,10-diazadecane (Note 5) as a slightly yellow oil which is sufficiently pure to be used for the preparation of N,N'-dibenzyl-4,13-diaza-18-crown-6.

B. *N,N'*-Dibenzyl-4,13-diaza-18-crown-6. In a 3-L, round-bottomed flask fitted with a mechanical stirrer and an efficient reflux condenser are placed 1,10-dibenzyl-4,7-dioxo-1,10-diazadecane (28.2 g, 86 mmol), 1,2-bis(2-iodoethoxy)ethane (39.3 g, 106 mmol) (Note 6), anhydrous sodium carbonate (45.3 g, 427 mmol), and sodium iodide (6.4 g, 43 mmol) in acetonitrile (1700 mL). The resulting solution is stirred mechanically (Note 7) and heated at reflux for 21 hr. The reaction is cooled, filtered, and concentrated under reduced pressure (Note 8). The crude solid is dissolved in a refluxing solution of acetone-dioxane (175 mL each) and allowed to crystallize in a freezer. The crystals (a mixture of sodium iodide and the sodium iodide complex of the product) are dried and taken up in 500 mL of water and 400 mL of chloroform. The phases are separated and the aqueous portion is extracted with chloroform (3 x 75 mL). The combined organic phases are dried (MgSO₄) and concentrated under reduced pressure. Recrystallization (hexanes, 500 mL, followed by absolute ethanol, 110 mL) affords 25.6-27.0 g (67-71%) of N,N'-dibenzyl-4,13-diaza-18-crown-6 as a white solid (mp 80-81°C); ¹H NMR (CDCl₃) δ: 2.82 (t, 8 H, NCH₂); 3.64 and 3.70 (t, s, s, 2 CH, OCH₂ and CH₂Ph); 7.37 (s, 10 H, Ar); IR (KBr) cm⁻¹: 2960, 2900, 2880, 1500, 1460, 1120, 1060, 1050, 750, 700 (Notes 9 and 10).

C. *4,13-Diaza-18-crown-6*. N,N'-Dibenzyl-4,13-diaza-18-crown-6 (25.0 g, 56 mmol) (Note 11), 10% Pd/C catalyst (1.0 g) and absolute ethanol (300 mL) are shaken in a Parr series 3900 hydrogenation apparatus at 60 psi hydrogen pressure and 25°C for 72 hr. The mixture is filtered through a pad of Celite and concentrated under reduced pressure. The yield of pure 4,13-diaza-18-

crown-6 after recrystallization (hexanes, 1 g/35 mL) is 13.5 g (91%). The white solid (mp 114-115°C) possesses physical properties identical to those previously reported:² ¹H NMR (CDCl₃) δ: 2.06 (bs, 2 H, NH); 2.72 (t, 8 H, CH₂N); 3.54 (t, s, 16 H, CH₂); IR (KBr) cm⁻¹: 3330.

2. Notes

1. Benzylamine was obtained from Aldrich Chemical Company, Inc., and was used without further purification.

2. 1,2-Bis(2-chloroethoxy)ethane was obtained from Eastman Kodak Company, and was used without further purification.

3. The excess benzylamine, recovered from the distillation step, can be reused if redistilled from calcium oxide.

4. If an efficient water aspirator is used (<20 mm), the benzylamine should distill between 60 and 70°C.

5. The product has the following spectral characteristics: ¹H NMR (CDCl₃) δ: 1.82 (s, 2 H, NH), 2.72 (t, 4 H, NCH₂), 3.58 (s and t, 8 H, CH₂), 3.72 (s, 4 H, benzyl), and 7.28 ppm (s, 10 H, Ar).

6. 1,2-Bis(2-iodoethoxy)ethane was prepared as described by Kulstad and Malmsten.³ 1,2-Bis(2-chloroethoxy)ethane (21.3 g, 0.114 mol) and sodium iodide (37.0 g, 0.247 mol) in acetone (55 mL) were heated at reflux while stirring magnetically during three days. The reaction mixture was allowed to cool, it was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride (200 mL), washed with aqueous 10% sodium thiosulfate solution (2 x 100 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The residual methylene chloride was removed by high vacuum evaporation at ambient

temperature and the resulting 1,2-bis(2-iodoethoxy)ethane (40 g, 95%) was used without further purification. The proton NMR spectrum (δ , CDCl_3) is as follows: 3.25 (t, 4 H); 3.68 (s, 4 H); 3.78 (t, 4 H).

7. This reaction must be stirred vigorously (120-150 rpm using a 60-mm paddle) for best results.

8. The acetonitrile in this step can be reused without any further purification.

9. Wester and Voegtle⁴ reported mp 80°C.

10. When this reaction is run on twice the reported scale, the percent yield is the same.

11. The N,N'-dibenzyl-4,13-diaza-18-crown-6 must be freshly recrystallized from absolute ethanol for the hydrogenolysis to proceed at a reasonable rate.

3. Discussion

During the past two decades, a relatively few macrocyclic polyethers have played central roles in numerous research programs. Examples are 18-crown-6, dibenzo-18-crown-6, and aza-15-crown-5. 4,13-Diaza-18-crown-6 and its derivatives are compounds of considerable current interest despite the parent's high price and limited availability. 4,13-Diaza-18-crown-6 is a key compound in the study of two-armed macrocycles since it may readily be alkylated or acylated to afford a variety of symmetrical, N,N'-disubstituted derivatives.

4,13-Diaza-18-crown-6 has been prepared in a variety of ways.^{2-3,5-9} Lehn first reported its preparation by reaction of 1,2-bis(2-aminoethoxy)ethane with triglycolic acid dichloride, followed by lithium aluminum hydride or diborane reduction of the resulting bislactam.² Kulstad and Malmsten have condensed 1,2-bis(2-aminoethoxy)ethane with 1,2-bis(2-iodoethoxy)ethane to give 4,13-diaza-18-crown-6.³ Recently, we have reported that a single-step reaction of benzylamine with 1,2-bis(2-iodoethoxy)ethane, followed by hydrogenation of the resulting N,N'-dibenzyl-protected crown, gives 4,13-diaza-18-crown-6.⁵ The latter, single-step cyclization reaction is more direct than the present procedure, but the yield is substantially lower and the manipulations are less convenient.

The method described here offers three advantages over the previously published procedures.^{2-3,5-9} First, the cyclization reaction does not require the use of high dilution conditions in order to obtain satisfactory yields of product. This is a substantial improvement over the procedure of Lehn² which requires large volumes of dry solvents and slow addition rates. Second, purification of all the intermediates is straightforward, involving either vacuum distillation using a Kugelrohr apparatus or recrystallization. This is an important advantage when the sequence is scaled up because it allows the preparation of large sample sizes in relatively short periods of time. We have prepared as much as 40 g of 4,13-diaza-18-crown-6 in less than 1 week. Third, the benzyl protecting groups are easily removed by hydrogenolysis over H₂/Pd-C in ethanol. Previous preparations of 4,13-diaza-18-crown-6 are more difficult because they involve the hydrolysis or reduction of N-tosyl protected nitrogens.⁵⁻⁸ We should also note that our own previously published,⁵ single-step preparation for N,N-disubstituted-4,13-diaza-18-crown-6 derivatives is more convenient than the present preparation because it

involves a single step reaction, but the yields are always inferior to those obtained using the present, multi-step approach.

1. Department of Chemistry, University of Miami, Coral Gables, FL 33124.
2. Dietrich, B.; Lehn, J. M.; Sauvage, J. P. *Tetrahedron Lett.* **1969**, 2885.
3. Kulstad, S.; Malmsten, L. A.; *Acta. Chem. Scand., Ser. B* **1979**, B55, 469.
4. Wester, N., Voegtle, F. *J. Chem. Res. (S)* **1978**, 400.
5. Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, 106, 8240.
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7. Desreux, J. F.; Renard, A.; Duyckaerts, G. *J. Inorg. Nucl. Chem.* **1977**, 59, 1587.
9. Bogatsky, A. V.; Lukyanenko, N. G.; Basok, S. S.; Ostrovskaya, L. K. *Synthesis* **1984**, 138.
9. Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, 96, 2268.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

4,13-Diaza-18-crown-6: 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane (8,9);
(23978-55-4)

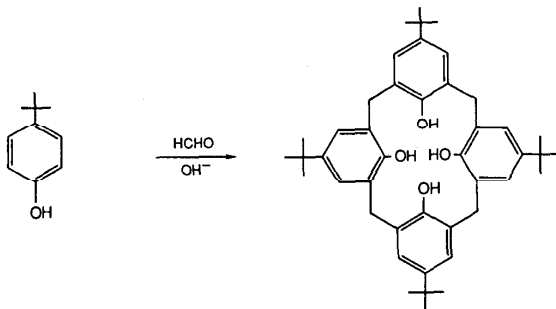
1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane: Benzenemethanamine,
N,N'-[1,2-ethanediylbis(oxy-2,1-ethanediyl)]bis- (10); (66582-26-1)

1,2-Bis(2-chloroethoxy)ethane: Ethane, 1,2-bis(2-chloroethoxy)- (8,9);
(112-26-5)

N,N'-Dibenzyl-4,13-diaza-18-crown-6: 1,4,10,13-Tetraoxa-7,16-
diazacyclooctadecane, 7,16-bis(phenylmethyl)- (10); (69703-25-9)

1,2-Bis(2-iodoethoxy)ethane: Ethane, 1,2-bis(2-iodoethoxy)- (9); (36839-55-1)

p-tert-BUTYL CALIX[4]ARENE



Submitted by C. D. Gutsche and M. Iqbal.¹

Checked by Anthony T. Watson and Clayton H. Heathcock.

1. Procedure

A. *Preparation of "precursor"*. A solution prepared from 100 g (0.666 mol) of p-tert-butylphenol, 62 mL of 37% formaldehyde solution (0.83 mol of HCHO), and 1.2 g (0.03 mol) of sodium hydroxide (corresponding to 0.045 equiv with respect to the phenol) (Note 1) is placed in a 3-L, three-necked flask equipped with a mechanical stirrer. The contents of the open flask are heated by means of a heating mantle (Note 2) for ca. 2 hr at 110-120°C. The reaction mixture, which is clear at the beginning, becomes viscous and turns yellow, eventually changing to a thick light yellow mass as the water evaporates (Note 3). During this period there is considerable frothing, and the reaction mixture may fill most of the flask before shrinking back to the original volume. The reaction vessel is removed from the heating mantle, allowed to

cool to room temperature, and 800-1000 mL of warm diphenyl ether is added to the flask to dissolve the residue. This process, which is facilitated by stirring, generally requires about 1 hr.

B. Pyrolysis of the precursor. The 3-L, three-necked flask is fitted with a nitrogen inlet. The contents of the flask are heated with a heating mantle while a stream of nitrogen is blown rapidly over the reaction mixture to facilitate the removal of the water that is evolved. During this period the color of the solution changes from yellow to light brown. When the evolution of water subsides and a solid starts to form (prior to attaining the reflux temperature) (Note 4) the flask is fitted with a condenser, and the contents of the flask are refluxed for 1.5-2 hr. During this phase of the reaction the solid dissolves, and a clear dark brown solution is formed. The reaction mixture is cooled to room temperature, and the product is precipitated by treatment with 1.5 L of ethyl acetate. The resulting mixture is stirred for 15-30 min and allowed to stand for at least 30 min (Note 5). Filtration yields material which is washed twice with 100-mL portions of ethyl acetate, once with 200 mL of acetic acid, and twice with 100-mL portions of water to yield ca. 66 g (61%) of crude product (Note 6). The beige-colored crude product is dissolved in ca. 1600-1800 mL of boiling toluene which is concentrated to ca. 700-900 mL. Upon cooling, 61 g (49%) of product is obtained as glistening white rhombic crystals, mp 342-344°C (Notes 7 and 8).

2. Notes

1. p-tert-Butylphenol from Aldrich Chemical Company, Inc., mp 98-101°C, and 37% formaldehyde solution from Fisher Chemical Company, Certified ACS grade, were used.

2. Care should be taken not to allow the heating mantle to get so hot as to char the solid material on the walls of the flask. Submitters have used an oil bath.

3. Stirring accelerates the rate of water removal, but is not necessary.

4. In some cases a solid does not form, and the solution remains clear throughout.

5. It may be convenient to transfer the contents of the three-necked flask to an Erlenmeyer flask prior to the addition of ethyl acetate.

6. The crude material is usually pure enough to be used in subsequent reactions without recrystallization.

7. The product is a 1:1 complex of p-tert-butylcalix[4]arene and toluene, from which the toluene can be removed by drying under high vacuum (>1 mm) and high temperature (>140°C) for an extended period of time (48 hr).

8. The melting point is measured in an evacuated melting point tube.

3. Discussion

A prototype of this procedure was first published in 1941 by Zinke and Ziegler,² although the unambiguous identity of the product was not established until some years later.³ A few other p-alkylcalix[4]arenes have been prepared by this procedure, but for practical purposes it appears to be restricted to p-alkylphenols in which the p-alkyl group is highly branched at the position adjacent to the phenyl ring. Thus, p-tert-pentylcalix[4]arene and p-(1,1,3,3-tetramethylbutyl)calix[4]arene⁴ are among the few other phenols that yield a tractable product in reasonable yield.

1. Department of Chemistry, Washington University, St. Louis, MO 63130.
2. Zinke, A.; Ziegler, E. *Ber.* **1941**, *74B*, 1729; Zinke, A.; Ziegler, E.; Martinowitz, E.; Pichelmayer, H.; Tomio, M.; Wittmann-Zinke, H.; Zwanziger, S. *Ber.* **1944**, *77B*, 264.
3. Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.
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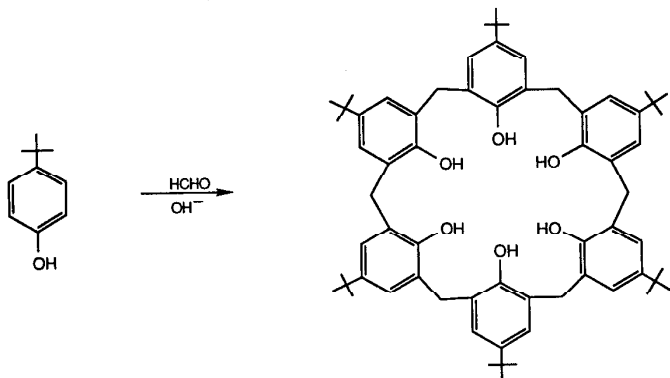
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

p-tert-Butylcalix[4]arene: Pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacos-
1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetraol,
5,11,17,23-tetrakis(1,1-dimethylethyl)- (10); (60705-62-6)

p-tert-Butylphenol: Phenol, p-tert-butyl- (8); Phenol, 4-(1,1-dimethylethyl)-
(9); (98-54-4)

p-tert-BUTYL CALIX[6]ARENE



Submitted by C. D. Gutsche, B. Dhawan, M. Leonis, and D. Stewart.¹

Checked by Roger J. Butlin and James D. White.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, and a Dean-Stark trap and condenser (Note 1), is placed in a Glas-Col heating mantle. To the flask are added 100 g (0.665 mol) of p-tert-butylphenol, 135 mL of 37% formalin solution (1.8 mol of HCHO), and 15 g (0.227 mol) of potassium hydroxide pellets (corresponding to 0.34 equiv of the phenol) (Notes 2 and 3). Heating and stirring are begun, and after 15 min nitrogen is blown across the reaction mixture at a brisk rate and out through the condenser on top of the Dean-Stark trap (Note 4); the reaction mixture is heated and stirred for 2 hr (Note 5). As the reaction progresses, the originally clear solution turns bright lemon yellow and as water is removed, the reaction mixture eventually changes to a thick, golden yellow mass of

taffy-like consistency (Note 6). During this period some frothing occurs, and the reaction mixture expands somewhat before shrinking to the original volume. Xylene (1 L) is now added to the flask to dissolve the semi-solid mass and give a yellow solution which is brought quickly to reflux by increasing the temperature of the heating mantle (Note 7). After 30 min a precipitate begins to form, and the color of the reaction mixture changes from yellow to orange. Refluxing is continued for 3 hr, the heating mantle is removed, and the mixture is allowed to cool to room temperature. The mixture is filtered, and the precipitate is washed with xylene and dried on a Büchner funnel to yield 105-110 g of crude, almost colorless product. This material is powdered, placed in an Erlenmeyer flask, dissolved in 2.5 L of chloroform (not completely soluble), and treated with 800 mL of 1 N hydrochloric acid. After 10-15 min the stirred solution turns yellow to light orange; stirring is continued an additional 10 min, and the mixture is transferred to a separatory funnel. The chloroform layer is drawn off, the aqueous layer is extracted with an additional 250 mL of chloroform, and the combined chloroform extracts are washed once with water and dried over magnesium sulfate. Magnesium sulfate is removed by filtration, the chloroform solution is concentrated to ca. 1 L by boiling, and 1 L of hot acetone is added to the boiling chloroform solution. The mixture is allowed to cool and is then filtered to give 90-95 g (83-88%) of product as a white powder: mp 372-374°C (Notes 8, 9, and 10).

2. Notes

1. It is not essential that a Dean-Stark trap be used. However, it provides a convenient way for monitoring this stage of the reaction and for collecting the aqueous formaldehyde mixture that is evolved.

2. *p*-tert-Butylphenol from Aldrich Chemical Company, Inc., mp 90-101°C, and 37% formaldehyde solution from Fisher Chemical Company, Certified ACS grade, were used. The potassium hydroxide (KOH) pellets are ca. 85% KOH and 15% water. When sodium hydroxide or lithium hydroxide is used instead of potassium hydroxide the yield of product is considerably lower.

3. Sometimes the reaction between the phenol and formaldehyde proceeds with sufficient speed after mixing that considerable warming takes place. Whether or not spontaneous warming occurs, the ultimate outcome of the reaction is the same.

4. Typically, the rate of nitrogen flow is ca. 200 bubbles/min, as measured by a bubbler attached to the condenser outlet. Although a rapid flow of nitrogen is not essential, it facilitates the removal of water and formaldehyde from the reaction mixture; this should amount to ca. 85 mL in the lower layer of the Dean-Stark trap.

5. Stirring is not absolutely necessary, but it accelerates the rate of removal of water. In unstirred reaction mixtures the frothing contents may fill the entire flask. Stirring reduces the amount of frothing.

6. As the reaction mixture becomes more viscous it is necessary to increase the torque on the stirring motor to keep the taffy-like mass in motion while heating is continued. It is important to remove as much of the water as possible in this first stage of the reaction by continuing the stirring as long as possible (see Note 7). When stirring becomes very difficult or when the yellow mass no longer sticks to the sides of the flask, xylene is added. Care should be taken not to scorch the reaction mixture at this point. As a further aid to rapid removal of water it is recommended that the upper portion of the reaction flask as well as the Dean-Stark trap be covered with insulating material such as cotton or glass wool.

7. Incomplete removal of water and/or too slow removal of water can result in the formation of a significant amount of cyclic octamer, which is difficult to separate from the cyclic hexamer. It is important, therefore, to bring the reaction mixture to reflux (10-15 min) and to remove all the water. In addition to the ca. 85 mL of H₂O/HCHO removed in the first phase of the reaction, an additional ca. 10 mL (as a cloudy, lower layer in the Dean-Stark trap) is removed in the second phase.

8. HPLC analysis of this product usually shows it to contain less than 1% of other calixarenes. If these are present in greater amounts (usually the cyclic tetramer, cyclic heptamer or cyclic octamer), their content can be reduced to less than 1% by triturating the product with hot acetone. The purity of the product can be qualitatively checked with TLC using a petroleum ether (30-60°C)/methylene chloride mixture (1:1) as eluant. The R_f of the cyclic hexamer is ca. 0.65, and the appearance of any spots with R_f greater than 0.1 indicates the presence of other calixarenes.

9. The melting point is measured in an evacuated and sealed melting point tube.

10. ¹H NMR spectrum (400 MHz, CDCl₃) δ: 1.29 (s, 54 H), 3.90 (s, 12 H), 7.16 (s, 12 H), 10.42 (s, 6 H).

3. Discussion

p-tert-Butylcalix[6]arene was first prepared by Gutsche, et al.² by the reaction of p-tert-butylphenol and paraformaldehyde in the presence of rubidium hydroxide (RbOH). A few other p-substituted calix[6]arenes have been prepared, including p-phenylcalix[6]arene³ and p-isopropylcalix[6]arene.⁴

1. Department of Chemistry, Washington University, St. Louis, MO 63130
2. Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.
3. Gutsche, C. D.; Pagoria, P. F.; *J. Org. Chem.* **1985**, *50*, 5795.
4. Dhawan, B.; Chen, S. I.; Gutsche, C. D. *Macromol. Chem.* **1987**, *188*, 921.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

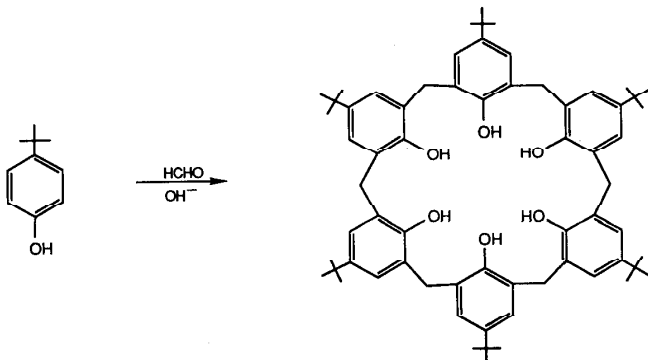
p-tert-Butylcalix[6]arene: Heptacyclo[31.3.1.1^{3,7}.1^{9,13}.1^{15,19}.-
1^{21,25}.1^{27,31}]octetraconta-1(37),3,5,7(42),9,11,13(41),15,17,-

19(40),21,23,25(39),27,29,31(38),33,35-octadecaene-37,38,39,40,41,42-
hexol,5,11,17,23,29,35-hexakis (1,1-dimethylethyl)- (10); [78092-53-2]

p-tert-Butylphenol: Phenol, p-tert-butyl- (8); Phenol, 4-(1,1-dimethylethyl)-
(9); (98-54-4)

Formaldehyde (8,9); (50-00-0)

p-tert-BUTYL CALIX[8]ARENE



Submitted by J. H. Munch^{1a} and C. D. Gutsche.^{1b}

Checked by Daniel T. Daly and James D. White.

1. Procedure

A slurry prepared from 100 g (0.67 mol) of p-tert-butylphenol, 35 g (ca. 1.1 mol) of paraformaldehyde (Note 1), and 2.0 mL (0.02 mol) of 10 N sodium hydroxide (Note 2) in 600 mL of xylene is placed in a 2-L, round-bottomed, three-necked flask fitted with a Dean-Stark water collector and a mechanical stirrer. The air in the flask is replaced with nitrogen, and the stirred contents of the flask are heated to reflux by means of a heating mantle. After 30 min a homogeneous solution is obtained, and after 1 hr a white precipitate begins to form. The reaction mixture is refluxed for 4 hr, the heating mantle is removed, the mixture is allowed to cool to room temperature, and the precipitate is removed by filtration. The crude product is washed, in succession, with 400-mL portions of toluene, ether, acetone, and water and is

then dried under reduced pressure. It is dissolved in ca. 1600 mL of boiling chloroform, the chloroform is concentrated to ca. 1200 mL, the solution is cooled to room temperature, and the precipitate is collected by filtration to yield 67-70 g (62-65%) of a colorless powder, dec 418-420°C (Notes 3 and 4).

2. Notes

1. p-tert-Butylphenol from Aldrich Chemical Company, Inc., mp 98-101°C, and paraformaldehyde from Fisher Chemical Company, Certified ACS grade, were used.

2. Other bases, including KOH, RbOH, and CsOH, also work with approximately the same results, but LiOH is considerably inferior.

3. The (solvated) product can be obtained in crystalline form but, upon standing in air for a few minutes, the colorless, glistening needles change to a white powder as the result of loss of solvent of crystallization. Considerable variation in the melting point of this material is noted. The product generally melts above 400°C, but sometimes the melting point falls to ca. 395°C or even lower. Undoubtedly, this is due to impurities which may be metal ions and/or other cyclic oligomers that are incompletely removed in the recrystallization (see Note 4).

4. Evaporation of the xylene filtrate and trituration of the residue with methylene chloride yields ca. 11 g of solid which consists mainly of cyclic hexamer and cyclic tetramer. The methylene chloride contains inter alia, cyclic pentamer, cyclic heptamer, and bishomo compound, and these can be obtained as pure samples in low yield by fractional crystallization procedures. The composition of the reaction mixtures can be qualitatively established by TLC by means of the following R_f values in 9:1 petroleum

ether/acetone and 1:1 petroleum ether/methylene-chloride, respectively: (a) cyclic octamer - 0.54, 0.85, (b) cyclic heptamer - 0.40, 0.78, (c) cyclic hexamer - 0.54, 0.76, (d) cyclic pentamer - 0.74, 0.68, (e) cyclic tetramer - 0.63, 0.66, and (f) bishomooxa compound - 0.66, 0.56.

3. Discussion

This method for preparing p-tert-butylcalix[8]arene was first described in the patent literature² by chemists of the Petrolite Corporation, St. Louis, MO and, therefore, is often referred to as the "Petrolite Procedure". It was introduced into journal literature by Gutsche, et al.³ Although the procedure is restricted to phenols substituted in the p-position with electronically neutral groups, it is more general in its application than the accompanying procedures for the calix[4]arenes and calix[6]arenes, and has been used with p-isopropylphenol,⁴ p-tert-pentylphenol,⁴ p-(1,1,3,3-tetramethylbutyl)phenol,⁵ and p-phenylphenol.⁶

1. (a) Petrolite Corporation, St. Louis, MO 63119; (b) Department of Chemistry, Washington University, St. Louis, MO 63130.
2. Buriks, R. S.; Fauke, A. R.; Munch, J. H. U.S. Patent 4 259 464, 1981; *Chem. Abstr.* **1981**, 94, P209, 722x.
3. Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, 103, 3782.
4. Dhawan, B.; Chen, S. I.; Gutsche, C. D. *Makromol. Chem.* **1987**, 188, 921.
5. Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Brit. J. Pharmacol.* **1955**, 10, 73.
6. Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, 50, 5795.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

p-tert-Butylcalix[8]arene: Nonacyclo[43.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}.1^{33,37}.1^{39,43}]hexapentaconta-1(49),3,5,7(56),9,11,13(55),15,17,19(54),21,23,25(53),27,29,31(52),33,35,37(51),39,41,43(50),45,47-tetracosaene-49,50,51,52,53,54,55,56-octol, 5,11,17,23,29,35,41,47-octakis(1,1-dimethylethyl)- (10); (68971-82-4)

p-tert-Butylphenol: Phenol, p-tert-butyl- (8); Phenol, 4-(1,1-dimethylethyl)- (9); (98-54-4)

Paraformaldehyde (9); (30525-89-4)

Unchecked Procedures

Accepted for checking during the period August 1, 1988
through May 1, 1989. An asterisk (*) indicates that
the procedure has been subsequently checked.

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Address requests to:

Professor Jeremiah P. Freeman
Organic Syntheses, Inc.
Department of Chemistry
University of Notre Dame
Notre Dame, Indiana 46556

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- 2460R* Enantioselective Saponification with Pig Liver Esterase (PLE)
(1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl Acetate
M. Eberle, M. Missbach, and D. Seebach,
Laboratorium für Organische Chemie, Eidgenössische Technische
Hochschule, Universitätstr. 16, CH - 8092 Zurich, Switzerland
- 2500* Hydromagnesiation Reaction of Propargylic Alcohols
F. Sato and Y. Kobayashi, Department of Chemical Engineering,
Tokyo Institute of Technology, Meguro, Tokyo 152, Japan
- 2501R A General Synthetic Method for the Oxidation of Primary Alcohols to
Aldehydes: S(+)-2-Methylbutanal
P. L. Anelli, F. Montanari, and S. Quici, Centro CNR and
Dipartimento di Chimica Organica e Industriale
dell'Università, Via Golgi 19, I-20133 Milano, Italy
- 2502* 1,3,4,6-Tetra-O-acetyl-2-deoxy- α -D-glucopyranose
B. Giese and K. S. Gröninger, Institut für Organische Chemie
und Biochemie der Technischen Hochschule, Petersenstrasse 22,
D-6100 Darmstadt, Federal Republic of Germany
- 2503R* Asymmetric Synthesis of 4,4-Dialkylcyclohexenones from Chiral
Bicyclic Lactams. (S)-4-Ethyl-4-allyl-2-cyclohexenone
A. I. Meyers and D. Berney, Department of Chemistry,
Colorado State University, Fort Collins, CO 80523
- 2504* 9-n-Butyl-1,2,3,4,5,6,7,8-Octahydroacridin-4-ol
T. W. Bell, Y.-M. Cho, A. Firestone, K. Healy, J. Liu, R. Ludwig and
S. D. Rothenberger, Department of Chemistry, State University of
New York at Stony Brook, Stony Brook, NY 11794-3400
- 2505* Methyl (Z)-3-(Phenylsulfonyl)-prop-2-enoate
G. C. Hirst and P. J. Parsons, Department of Chemistry
University of California, Irvine, Irvine, CA 92717
- 2506* Lipase Catalyzed Kinetic Resolution of Alcohols via Chloroacetate
Esters: (-)-(1R,2S)-trans-2-Phenylcyclohexanol and (+)-(1S,2R)-
trans-2-Phenylcyclohexanol
A. Schwartz, P. Madan, J. K. Whitesell, and R. M. Lawrence,
Department of Chemistry, University of Texas, Austin,
Austin, TX 78712
- 2507* A Useful Fluorinating Agent, N-Fluoropyridinium Triflate, and α -
Fluorination of a Ketone
T. Umemoto, K. Tomita, and K. Kawada, Sagami Chemical Research
Center, Nishi-Onuma 4-4-1, Sagamihara, Kanagawa 229, Japan
- 2510 Intramolecular Oxidative Coupling of a Disenolate: 4-
Methyltricyclo[2.2.2.0^{3,5}]octane-2,6-dione
M.-A. Poupart, G. Lassalle, and L. A. Paquette, Department of
Chemistry, The Ohio State University, Columbus, OH 43210

- 2511* Mixed Higher Order Cyanocuprate-Induced Epoxide Openings:
1-Benzoyloxy-4-penten-1-ol
B. H. Lipshutz, R. Moretti, and R. Crow, Department of Chemistry
University of California, Santa Barbara, CA 93106
- 2512* A General Method for the Preparation of 9-, 10-, and 11-Membered
Unsaturated Macrolides: Synthesis of 8-Propionyl-E-5-nonenolide
K. S. Webb, E. Asirvatham, and G. H. Posner, Department of Chemistry
The Johns Hopkins University, Baltimore, MD 21218
- 2513* The Conversion of Esters to Allylsilanes: Trimethyl(2-methylene-4-
phenyl-3-butenyl)silane
W. H. Bunnelle and B. A. Narayanan, Department of Chemistry
University of Missouri, Columbia, MO 65211
- 2514* Alkynyl(phenyl)iodonium Tosylates: Preparation and Stereospecific
Coupling with Vinylcopper Reagents. Formation of Conjugated Enynes
P. J. Stang and T. Kitamura, Department of Chemistry
University of Utah, Salt Lake City, UT 84112
- 2515 Diazoketone Cyclization onto a Benzene Ring: 3,4-Dihydro-1(2H)-
Azulenone
L. T. Scott and C. A. Sumpter, Department of Chemistry
University of Nevada-Reno, Reno, NV 89557-0020
- 2516 Oxidation of Secondary Amines to Nitrones: 6-Methyl-2,3,4,5-
Tetrahydropyridine N-Oxide
S.-I. Murahashi, T. Shiota, and Y. Imada, Department of Chemistry
Faculty of Engineering Science, Osaka University
Machikaneyama, Toyonaka, Osaka, Japan 560
- 2518 Preparation of (E,Z)-1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-
pentadiene
D. C. Myles and M. H. Bigham, Department of Chemistry
Yale University, New Haven, CT 06511
- 2519* Synthesis of β -Ketoesters by C-Acylation of Preformed Enolates with
Methyl Cyanoformate: Preparation of (1 α ,4 β ,8 $\alpha\alpha$)Methyl 2 Oxo
decahydro-1-naphthoate
S. R. Crabtree, L. N. Mander, and S. P. Sethi, Research School of
Chemistry, Australian National University, GPO Box 4
Canberra, A.C.T. 2601, Australia
- 2520 9-Thiabicyclo[3.3.1]nonane-2,6-dione
R. Bishop, School of Chemistry, The University of New South Wales
P.O. Box 1, Kensington, New South Wales, Australia 2033
- 2521 Synthesis of N-Protected α -Amino Acids from N-(Benzyloxycarbonyl)-L-
Serine via Its β -Lactone: N²-(Benzyloxycarbonyl)- β -(Pyrazol-1-yl)-
L-Alanine
S. V. Pansare, G. Huyer, L. D. Arnold, and J. C. Vederas, Department
of Chemistry, University of Alberta, Edmonton, Alberta,
Canada T6G 2G2

- 2523 2-(2,2-Dimethoxyethyl)cyclopentanone
E. Baciocchi and R. Ruzziconi, Dipartimento di Chimica,
Universita di Perugia, 06100 Perugia, Italy
- 2524 Preparation of Enantiomerically Pure (2R)- and (2S)-Ethyl-2-
Fluorohexanoate by Enzyme-Catalyzed Kinetic Resolution
P. Kalaritis and R. W. Regenye, Abbott Laboratories,
Bldg. R1B, Rm. 2047, N. Chicago, IL 60064
- 2526 2-Substituted Pyrroles from N-tert-Butoxycarbonyl-2-bromopyrrole:
N-tert-Butoxy-2-trimethylsilylpyrrole
W. Chen, E. K. Stephenson, and M. P. Cava, Department of Chemistry,
University of Alabama, Tuscalousa, AL 35487
- 2528 (E)-1-Benzyl-3-(1-Iodoethylidene)piperidine: Nucleophile-Promoted
Alkyne-Iminium Ion Cyclizations
H. Arnold, L. E. Overman, M. J. Sharp, and M. C. Witschel,
Department of Chemistry, University of California, Irvine,
Irvine, CA 92717
- 2530 2-Cyano-6-phenyloxazolopiperidine
M. Bonin, D. S. Grierson, J. Royer, and H.-P. Husson,
Institut de Chimie des Substances, Naturelles du C.N.R.S.,
91198 Gif-sur-Yvette Cedex, France
- 2531 1,1-Dimethylethyl (S)- or (R)-4-Formyl-2,2-dimethyl-3-
oxazolidinecarboxylate: A Useful Serinal Derivative
P. Garner and J. M. Park, Department of Chemistry,
Case Western Reserve University, Cleveland, OH 44106

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 - e. How determined?
- 6) Any unusual apparatus or experimental technique:
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- 8) Source of starting material?
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ORGANIC SYNTHESES

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OF ORGANIC CHEMICALS

VOLUME 69

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society, The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60-64 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which has appeared as *Collective Volume Seven* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Syntheses Proposal Format

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- 6) a. Proposed scale, final product:
b. Overall yield:
c. Method of isolation and purification:
d. Purity of product (%):
e. How determined?
- 7) Any unusual apparatus or experimental technique:
- 8) Any hazards?
- 9) Source of starting material?
- 10) Utility of method or usefulness of product.

Submit to: Dr. Jeremiah P. Freeman, Secretary
Department of Chemistry
University of Notre Dame
Notre Dame, IN 46556

Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Hoffmann-La Roche, Inc., Merck & Co. and the Rohm and Haas Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

PREFACE

Like its predecessors, this volume contains checked and edited procedures dealing with important new synthetic methods or specific compounds holding potential interest for synthetic chemists. The compilation begins with three procedures detailing kinetic resolution by enzymatic means. Of these, the preparations of **(-)-(1R,2S)-** and **(+)-(1S,2R)-trans-2-PHENYLCYCLOHEXANOL** and **ETHYL (R)-** and **(S)-2-FLUOROHEXANOATE** rely on lipase-catalyzed ester hydrolysis. The use of pig liver esterase for enantioselective saponification is nicely demonstrated in the case of **(1S,2S,3R)-3-HYDROXY-2-NITROCYCLOHEXYL ACETATE**. The next group of entries constitute a cluster of five stereocontrolled processes that have proven useful for constructing relative complex molecules. In the first, which targets **(4RS,4aRS,6RS,8aRS)-**, **(4S,4aS,6S,8aS)-**, and **(4R,4aR,6R,8aR)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a-OCTAHYDRO-2,3-BENZOPYRONE**, an intramolecular Diels-Alder reaction is responsible for the diastereoselectivity. The stereoselective 1,4-functionalization of 1,3-dienes is exemplified by a two-step process leading to **cis- and trans-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE**. The effectiveness of a silyl hydride in providing a means for erythro-directed reduction of a β -keto amide is applied in a route to **ERYTHRO-1-(3-HYDROXY-2-METHYL-3-PHENYL-PROPANOYL)PIPERIDINE**. This is followed by an asymmetric synthesis based on a chiral bicyclic lactam leading to **(R)-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE**. The stereoselectivity with which acetoxy migration can operate to an adjacent radical center is reflected in the one-step reaction that gives rise to **1,3,4,6-TETRA-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSE**.

The third set of procedures focuses on the vital role that organometallic reagents play in the transformation of functional groups. The first of the seven

illustrative examples provides details on the use of the *Tebbe reagent* for effecting the methylenation of esters. The two model systems are **1-PHENOXY-1-PHENYLETHENE** and **3,4-DIHYDRO-2-METHYLENE-2H-1-BENZOPYRAN**. In a similar vein, the efficacy with which mixed higher-order cyanocuprates can realize the opening of epoxides is demonstrated in the preparation of **1-BENZYLOXY-4-PENTEN-2-OL**. Silicon-containing Grignard reagents are rapidly being developed as versatile and utilitarian reagents. In this context, the procedure to make **TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE** is a specific example of a one-step conversion of esters to allylsilanes. The readiness with which the nucleophilic hydroxymethylation of carbonyl compounds can be realized is illustrated by the formation of **1-(HYDROXYMETHYL)CYCLOHEXANOL**. A different use of Grignard chemistry is reflected in the hydromagnesiation of propargylic alcohols to afford **(E)-3-PENTYL-2-NONENE-1,4-DIOL**. New uses of lithium organometallics are illustrated in conjunction with *in situ* generation of acyllithium reagents from carbon monoxide as used in making **3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE**, and with the propargylation of alkyl halides as employed for gaining access to **(E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE** and **(E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL**.

The next cluster of seven procedures is grouped together in line with the long-standing *Organic Syntheses* tradition of providing preparations of starting materials that play an established role in important structural transformations and/or multistep syntheses. **N-FLUOROPYRIDINIUM TRIFLATE**, a versatile electrophilic fluorinating agent, is one such material. The companion preparations of **1-CHLORO-1-(TRICHLOROETHYL)CYCLOPROPANE** and **METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE** describe reliable entry to useful three-membered ring building blocks. The next two procedures address the preparation of **(+)-(2R,8aS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE**, a selective, aprotic

oxidizing agent of considerable importance, and **(-)-D-2,10-CAMPHORSULTAM**, a chiral auxiliary that has found substantial use in asymmetric reactions of various types. A high-yielding, one-step route to highly functionalized sulfonyl acrylates is demonstrated by the preparation of **METHYL (Z)-3-(BENZENESULFONYL)-PROP-2-ENOATE**, a useful dienophile.

The next six procedures have a strong methodological bent. Thus, the pathway to **4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE** is based on effective intramolecular oxidative coupling of a bisenolate. The preparation of **3,4-DIHYDRO-(2H)-AZULENONE** exemplifies the ability of a diazo ketone to undergo intramolecular cyclization onto an aromatic ring. A concise, four-component condensation forms the basis for a general unsaturated macrolide synthesis as illustrated for **8-PROPIONYL-(E)-5-NONENOLIDE**. The practicality of engaging keteniminium salts and chlorocyanoketene in efficient [2+2] cycloadditions is demonstrated by procedures leading to **3-HEXYLCYCLOBUTANONE** and **7-CHLORO-7-CYANOBICYCLO[4.2.0]OCTAN-8-ONE**. A catalytic means for oxidizing alcohols with oxammonium salts is employed for obtaining **(S)-(+)-2-METHYLBUTANAL**.

The volume concludes with three convenient procedures to make functionalized molecules having varied applications: **5,6-DIETHOXYBENZOFURAN-4,7-DIONE**, **9-n-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL**, and **ETHYL 3,3-DIETHOXYPROPANOATE**.

The long-time standards of *Organic Syntheses* to provide for use by experimental organic chemists a collection of carefully checked, useful procedures have been extended to this volume thanks to the unstinting efforts of many individuals. Certainly, the members of the Boards of Editors and their students whose names are cited herein garner a large share of my appreciation for their time-consuming efforts in carrying out the rigorous protocols associated with checking the procedures. The

entire effort has been greatly facilitated by the impressive organizational skills of Professor Jeremiah P. Freeman, the Secretary to the Board. Finally, the production of the final product is largely attributed to his expertise and that of Dr. Theodore W. Greene, our Assistant Editor, whose painstaking efforts with the textual material provide the very attractive and readable text that is before you.

Columbus, Ohio

Leo A. Paquette

March 1990



MAX TISHLER

October 30, 1906 - March 17, 1989

Max Tishler combined, to an exceptional degree, excellence in two seemingly diverse areas. He was a giant in advanced and sophisticated medicinal chemistry research and an administrator with a remarkably inspirational gift for teaching and academic leadership. On the one hand, Tishler pioneered the round-the-clock system for pressure research at Merck. Later, he became the quintessential undergraduate and graduate mentor at Wesleyan University. A distinguished career in industry culminated as President of Merck, Sharpe & Dohme Research Laboratories. Tishler was Editor-in-Chief of Volume 39 of *Organic Syntheses*, which was published in 1959.

Max Tishler was born in Boston on October 30, 1906. He received the B.S. in 1928 from Tufts College, and the M.A. from Harvard in 1933 while working part-time as a pharmacist. The Ph.D. degree was awarded in 1934 by Harvard. After scientific collaboration with E. P. Kohler and J. B. Conant, he joined Merck & Company, Inc. Research Laboratories in 1937. After retiring from Merck, Dr. Tishler was appointed Professor of Chemistry at Wesleyan University in Middletown, Connecticut (1970 - 1972); University Professor of Sciences (1972 - 1975); and Emeritus (1975 - 1989).

Dr. Tishler published more than 100 scientific papers and is cited as an inventor on more than 100 United States patents. A partial list of research contributions include development of processes for the commercial production of vitamin B6, vitamin K, vitamin E, penicillin, streptomycin, and cortisone.

Dr. Tishler was very active in the American Chemical Society, serving for many years on the Board of Directors and as President in 1972. He received the Priestley Medal of the ACS in 1970. He was a member of the National Academy of Sciences. Tishler received an honorary Sc.D. from Tufts University in 1956 and a D.Eng. from Stevens Institute of Technology in 1966. In 1987, he received the National Medal of Science.

An anecdote illustrates Tishler's drive. The total synthesis of cortisone, as devised by Lewis Sarrett, comprised approximately 30 steps and required weeks of intense and painstaking effort. Max was in charge of the first commercial production of cortisone in the pilot plant. One of the final steps is the isomerisation of a double bond into conjugation with the 3-ketone function with the formation of a 2,4-dinitrophenylhydrazone, causing the development of a brilliant, scarlet color. Tishler was inspecting the first production run. To his horror, he spotted a bright-red liquid leaking near the vessel. "I hope that's blood!", he exclaimed. Actually, Max was very concerned for individuals, beneath a rather formidable exterior.

A story of my contacts with Max Tishler after my Merck days is worth recounting. My MIT group was busily preparing 100-gram quantities of penicillamine for use in our penicillin synthesis program. A Professor of Chemical Medicine at Harvard, Dr. Charles Davidson, and a British medical colleague requested a sample of penicillamine for their experimental program relating to sequestering copper ion. About one year later, my MIT telephone started jumping off the hook, frantic telegrams arrived, and one anxious visitor was at my door. It seems that an article had appeared in the British medical journal, *Lancet*, reporting that penicillamine was very helpful in the symptomatic treatment of Wilson's Syndrome, a disorder characterized by the accumulation of cupric ion in the brain. In a footnote, "Prof. John C. Sheehan of MIT" was credited with furnishing the penicillamine. The visitor at my office was offering to pay almost any price since his son suffered from the disease. I told him that not only could I not sell the compound, but I could not even give any away, even to his physician, since it was not approved by the FDA.

I telephoned Max Tishler, outlined the situation, and he said he would call back that afternoon. Max contacted the Merck Medical Department, who stated that Wilson's Syndrome was a rare condition affecting only about 50 to 100 patients a year, and was terminal. However, Max was able to launch a crash program to prepare penicillamine at Merck and get quick FDA approval under the "orphan disease" category, in spite of the unpromising commercial outlook.

He is survived by his wife, Elizabeth (Betty) Tishler (married in 1934) and two sons -- Peter Vermeer Tishler and Carl Lewis Tishler.

June 4, 1990

John C. Sheehan

CONTENTS

A. Schwartz, P. Madan, J. K. Whitesell, and R. M. Lawrence	1	LIPASE-CATALYZED KINETIC RESOLUTION OF ALCOHOLS VIA CHLOROACETATE ESTERS: (-)- (1R,2S)-trans-2-PHENYLCYCLO- HEXANOL AND (+)-(1S,2R)-trans- 2-PHENYLCYCLOHEXANOL
P. Kalaritis and R. W. Regenye	10	ENANTIOMERICALLY PURE ETHYL (R)- AND (S)-2-FLUORO- HEXANOATE BY ENZYME- CATALYZED KINETIC RESOLUTION
Martin Eberle, Martin Missbach, and Dieter Seebach	19	ENANTIOSELECTIVE SAPONIFICATION WITH PIG LIVER ESTERASE (PLE): (1S,2S,3R)- 3-HYDROXY-2- NITROCYCLOHEXYL ACETATE
L. F. Tietzø, G. v. Kiedrowski, K.-G. Fahlbusch, and E. Voss	31	DIASTEREOSELECTIVE FORMATION OF α -METHOXYCARBONYL LACTONES THROUGH AN INTRAMOLECULAR DIELS-ALDER REACTION: (4RS,4aRS,6RS,8aRS)-, (4S,4aS,6S,8aS)- AND (4R,4aR,6R,8aR)-4-METHOXY- CARBONYL-1,1,6-TRIMETHYL- 1,4,4a,5,6,7,8,8a-OCTAHYDRO- 2,3-BENZOPYRONE [rac-5, (+)-5, and (-)-5]
Jan-E. Bäckvall and Jan Vågberg	38	STEREOSELECTIVE 1,4-FUNCTIONAL- IZATIONS OF CONJUGATED DIENES: cis- and trans-1-ACETOXY-4- (DICARBOMETHOXYMETHYL)-2- CYCLOHEXENE
M. Fujita and T. Hiyama	44	ERYTHRO-DIRECTED REDUCTION OF OF A β -KETO AMIDE: ERYTHRO- 1-(3-HYDROXY-2-METHYL-3- PHENYLPROPANOYL)PIPERIDINE
Albert I. Meyers and Daniel Berney	55	ASYMMETRIC SYNTHESIS OF 4,4- DIALKYL CYCLOHEXENONES FROM CHIRAL BICYCLIC LACTAMS: (R)-4- ETHYL-4-ALLYL-2-CYCLOHEXEN- 1-ONE

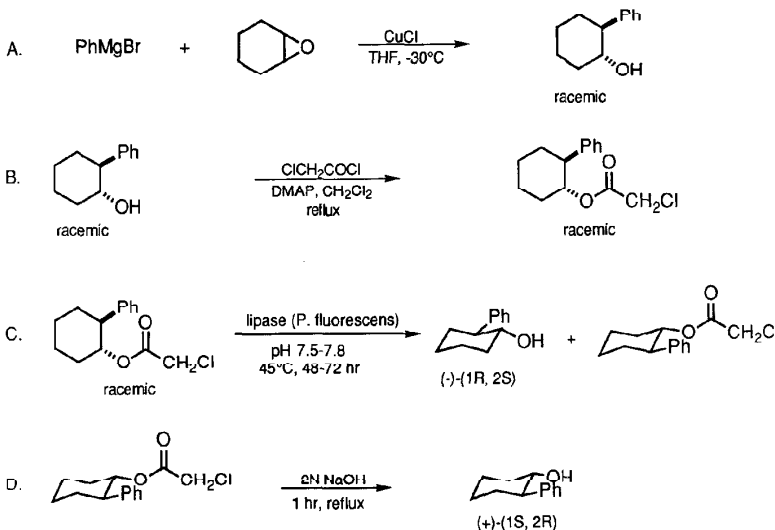
Bernd Giese and Kay S. Gröninger	66	1,3,4,6-TETRA-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSE
Stanley H. Pine, Gia Kim, and Virgil Lee	72	THE SYNTHESIS OF ENOL ETHERS BY METHYLENATION OF ESTERS: 1-PHENOXY-1-PHENYLETHENE AND 3,4-DIHYDRO-2-METHYLENE-2H-1-BENZOPYRAN
Bruce H. Lipshutz, Robert Moretti, and Robert Crow	80	MIXED HIGHER ORDER CYANOCUPRATE-INDUCED EPOXIDE OPENINGS: 1-BENZYLOXY-4-PENTEN-2-OL
William H. Bunnelle and B. A. Narayanan	89	THE CONVERSION OF ESTERS TO ALLYLSILANES: TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE
Kohei Tamao, Neyoshi Ishida, Yoshihiko Ito, and Makoto Kumada	96	NUCLEOPHILIC HYDROXY-METHYLATION OF CARBONYL COMPOUNDS: 1-(HYDROXY-METHYL)CYCLOHEXANOL
Fumie Sato and Yuichi Kobayashi	106	HYDROMAGNESIATION REACTION OF PROPARGYLIC ALCOHOLS: (E)-3-PENTYL-2-NONENE-1,4-DIOL FROM 2-OCTYN-1-OL
Richard Hui and Dietmar Seyferth	114	DIRECT NUCLEOPHILIC ACYLATION BY THE LOW TEMPERATURE, IN SITU GENERATION OF ACYL-LITHIUM REAGENTS; α -HYDROXY KETONES FROM KETONES: 3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE FROM PINACOLONE
John Hooz, Jorge Cabezas, Sergio Musmanni, and Jose Calzada	120	PROPARGYLATION OF ALKYL HALIDES: SYNTHESIS OF (E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE AND (E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL
Teruo Umemoto, Kyoichi Tomita, and Kosuke Kawada	129	N-FLUOROPYRIDINIUM TRIFLATE: AN ELECTROPHILIC FLUORINATING AGENT

Thomas Liese, Frank Jaekel, and Armin de Meijere	144	1-CHLORO-1-(TRICHLORO- ETHENYL)CYCLOPROPANE
Thomas Liese, Fereydoun Seyed-Mahdavi, and Armin de Meijere	148	METHYL 2-CHLORO-2-CYCLO- PROPYLIDENACETATE
Michael C. Weismiller, James C. Towson, and Franklin A. Davis	154	SYNTHESIS OF (-)-D-2,10- CAMPHORSULTAM
James C. Towson, Michael C. Weismiller, G. Sankar Lal, Aurelia C. Sheppard, and Franklin A. Davis	158	SYNTHESIS OF (+)-(2R,8aS)-10- (CAMPHORYLSULFONYL)OXA- ZIRIDINE
G. C. Hirst and P. J. Parsons	169	METHYL (Z)-3-(BENZENESULFONYL PROP-2-ENOATE
Marc-André Poupart, Gilbert Lassalle, and Leo A. Paquette	173	INTRAMOLECULAR OXIDATIVE COUPLING OF A BIENOLATE: 4-METHYLTRICYCLO[2.2.2.0 ^{3,5}]- OCTANE-2,6-DIONE
Lawrence T. Scott and Chris A. Sumpter	180	DIAZO KETONE CYCLIZATION ONTO A BENZENE RING: 3,4-DIHYDRO-1(2H)-AZULENONE
Kevin S. Webb, Edward Asirvatham, and Gary H. Posner	188	A GENERAL METHOD FOR THE PREPARATION OF 9-, 10-, AND 11- MEMBERED UNSATURATED MACROLIDES: SYNTHESIS OF 8-PROPIONYL-(E)-5-NONENOLIDE
C. Schmit, J. B. Falmagne, J. Escudero, H. Vanlierde, and L. Ghosez	199	A GENERAL SYNTHESIS OF CYCLOBUTANONES FROM OLEFINS AND TERTIARY AMIDES: 3-HEXYLCYCLOBUTANONE
Paul L. Fishbein and Harold W. Moore	205	7-CHLORO-7-CYANOBI-CYCLO- [4.2.0]OCTAN-8-ONE
Pier Lucio Anelli, Fernando Montanari, and Silvio Quici	212	A GENERAL SYNTHETIC METHOD FOR THE OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES: (S)-(+)-2-METHYLBUTANAL

S. T. Perri, P. Rice, and H. W. Moore	220	REARRANGEMENT OF 4-ARYL-4- HYDROXY-2,3-DIALKOXYCYCLO- BUTENEDIONES TO ANNULATED HYDROQUINONES AND QUINONES: 5,6-DIETHOXYBENZOFURAN-4,7- DIONE
Thomas W. Bell, Young-Moon Cho, Albert Firestone, Karin Healy, Jia Liu, Richard Ludwig and Scott D. Rothenberger	226	9-n-BUTYL-1,2,3,4,5,6,7,8- OCTAHYDROACRIDIN-4-OL
L. F. Tietze, E. Voss, and U. Hartfiel	238	SYNTHESIS OF ALKYL PROPANOATES BY A HALOFORM REACTION OF A TRICHLORO KETONE: PREPARATION OF ETHYL 3,3-DIETHOXYPROPANOATE
Unchecked Procedures	245	
Cumulative Author Index for Volumes 65, 66, 67, 68, and 69	249	
Cumulative Subject Index for Volumes 65, 66, 67, 68, and 69	254	

**LIPASE-CATALYZED KINETIC RESOLUTION OF ALCOHOLS VIA
CHLOROACETATE ESTERS: (-)-(1R,2S)-trans-2-
PHENYLCYCLOHEXANOL AND (+)-(1S,2R)-trans-2-
PHENYLCYCLOHEXANOL**

**(Cyclohexanol, 2-phenyl-, (1R-trans)- and cyclohexanol, 2-phenyl-,
(1S-trans)-)**



Submitted by A. Schwartz,¹ P. Madan,¹ J. K. Whitesell,² and R. M. Lawrence.²

Checked by Robert E. Maleczka, Jr. and Leo A. Paquette.

1. Procedure

A. *Racemic trans-2-phenylcyclohexanol*. A 3-L, round-bottomed flask equipped with a mechanical stirrer, addition funnel, reflux condenser, and nitrogen inlet is charged with 35.3 g (1.47 g-atom) of magnesium turnings (Note 1) and 170 mL of dry tetrahydrofuran (THF). To this stirred mixture a solution of 155 mL (1.47 mol) of bromobenzene (Note 2) in 250 mL of dry THF is added dropwise over a 1.5-hr period (Notes 3 and 4). After the addition of bromobenzene is complete, 1 L of dry THF is added. The solution is cooled to -30°C (dry ice-nitromethane slush bath) and 6.53 g (0.066 mol) of purified (Note 5) copper(I) chloride is added. The resulting mixture is stirred for 10 min and then a solution of 101 mL (1.0 mol) of cyclohexene oxide (Note 6) in 100 mL of THF is added dropwise over a 1.5-hr period. Upon completion of the addition, the reaction mixture is allowed to warm to 0°C and stirred for 2 hr, then quenched by adding 500 mL of saturated ammonium sulfate $[(\text{NH}_4)_2\text{SO}_4]$ solution (aqueous). The layers are separated and the organic layer is washed with 100 mL of saturated $(\text{NH}_4)_2\text{SO}_4$ (Note 7). The combined aqueous layers are extracted with ether, the organic layers are combined and dried over anhydrous MgSO_4 , and the solvent is removed via rotary evaporator to give 175.5 g (99.6% crude) of the desired product as a light yellow solid. The solid is recrystallized from pentane to give 142.3 g (80%), mp $55.5\text{--}57.0^{\circ}\text{C}$ (lit.¹² $57\text{--}58^{\circ}\text{C}$) (Note 8).

B. *Racemic trans-2-phenylcyclohexyl chloroacetate*. A 1-L, round-bottomed flask equipped with a magnetic stirrer and a condenser is charged with 100 g (0.567 mol) of racemic trans-2-phenylcyclohexanol, 50 mL (0.625 mol) of chloroacetyl chloride (Note 9), 300 mg (0.0025 mol) of 4-dimethylaminopyridine (DMAP) (Note 10) and 250 mL of dichloromethane. This mixture is rapidly stirred and heated at reflux for 6 hr. The mixture is cooled and a solution of 350 mL of saturated sodium bicarbonate is carefully added to the rapidly stirring mixture (Note 11). Stirring is maintained for 3

hr (Note 12). The organic layer is separated and dried over anhydrous potassium carbonate. After filtration the filtrate is concentrated on a rotary evaporator (30°C) to a dark brown oil. This oil is distilled through a 2"- or 4"-column packed with glass beads to give, after collecting a small forerun (ca. 2 g), 135 g (94%) of racemic trans-2-phenylcyclohexyl chloroacetate as a colorless liquid, bp 118-122°C/0.3 mm.

C. (-)-(1*H*,2*S*)-trans-2-Phenylcyclohexanol. A 500-mL, three-necked Morton flask (Note 13) equipped with a mechanical stirrer, pH probe (connected to a pH controller, Note 14) and a base inlet (connected to a syringe pump regulated by the pH controller and a calibrated 250-mL reservoir (Note 15) of 1 N sodium hydroxide) is charged with 106.0 g (0.419 mol) of racemic trans-2-phenylcyclohexyl chloroacetate, 10 mL of pH 7 buffer (Note 16), and 90 mL of deionized water. This heterogeneous mixture is rapidly stirred and heated to between 45°C and 50°C using a constant temperature bath. The pH is adjusted to 7.5 with 1 N sodium hydroxide and after a steady pH reading is achieved (Note 17), 1 g of lipase (*P. fluorescens*, Note 18) is added. Immediately 1 N sodium hydroxide begins to flow into the reaction mixture as the pH begins to drop (indicating hydrolysis of the chloroacetate). The pH controller regulates the addition of base so as to maintain the pH between 7.5 and 7.8. After 2 hr, an additional 1.5 g of lipase is added to the reaction mixture and the rate of hydrolysis becomes noticeably faster (Note 19). After 45 hr, ~200 mL (~95% of theory) of 1 N sodium hydroxide has been added and the rate of hydrolysis has become very slow. After ~50 hr, 210 mL of 1 N sodium hydroxide (0.21 mol, 100% of theory) has been added to the mixture and the rate of base addition has nearly stopped (Note 20). The mixture is cooled to room temperature and extracted with three 200-mL portions of ether. The organic layer is filtered through a small pad of Celite to remove traces of enzyme emulsion and the Celite is rinsed with three 100-mL portions of ether. The combined organic layers are dried over anhydrous sodium sulfate and after filtration are concentrated on a rotary evaporator (35°C) and finally dried at 0.5 mm for 1 hr to

give 93 g of a colorless oil. Fractional crystallization from 100 mL of petroleum ether (30-60°C) at -20°C (freezer) overnight affords 19.8 g (53.5% of theory, Note 21) of (-)-(1R,2S)-trans-2-phenylcyclohexanol as colorless needles, mp 63-65°C, $[\alpha]_{\text{D}}^{25} -54.3^\circ$ (methanol, *c* 18). An additional 15.8 g of the (-) alcohol is obtained by chromatography of the mother liquors (vide infra) to afford a total of 35.6 g (96.2% of theory, Notes 21 and 22).

The mother liquors are concentrated on a rotary evaporator (35°C) to give a colorless oil that is redissolved in 100 mL of hexanes and poured onto a 250-g pad of silica gel (Note 23) contained in a 500-mL sintered glass funnel, pre-equilibrated with hexanes. Using this simple silica pad, 100-mL fractions are collected, diluting first with 1 L of hexanes, followed by 3 L of 9:1 hexanes:ethyl acetate, and finally with 600 mL of ethyl acetate. After TLC analysis of the eluants (Note 24), fractions 3-18 are combined and concentrated initially on a rotary evaporator (40°C) and finally dried at 0.5 mm to afford 52.0 (98% of theory) of (-)-(1S,2R)-trans-2-phenylcyclohexyl chloroacetate as a colorless oil, $[\alpha]_{\text{D}}^{25} -14.3^\circ$ (benzene, *c* 10). Fractions 20-28 are combined and concentrated as above to afford 15.8 g of the (-)-(1R,2S)-trans-2-phenylcyclohexanol, mp 62-65°C, $[\alpha]_{\text{D}}^{25} -54.9^\circ$ (methanol, *c* 2.1).

D. (+)-(1S,2R)-trans-2-Phenylcyclohexanol. A 500-mL, round-bottomed flask is charged with a mixture of 52.0 g (0.206 mol) of (+)-(1S,2R)-trans-2-phenylcyclohexyl chloroacetate, 250 mL of 2 N sodium hydroxide, and 100 mL of methanol and then stirred at reflux for 3 hr. TLC analysis (Note 24) indicates complete reaction. The mixture is cooled to room temperature, adjusted to pH 7 with ~35 mL of 3 N sulfuric acid and poured into 500 mL of water. The mixture is extracted with two 150-mL portions of dichloromethane and the organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator (35°C) to afford 37.0 g of a colorless solid. Recrystallization from 100 mL of petroleum ether (30-60°C) at -20°C gives in

two crops, 35.8 g (96% of theory) of (+)-(1S,2R)-trans-2-phenylcyclohexanol as colorless needles, mp 60-62°C, $[\alpha]_D^{25} +52.8^\circ$ (methanol, c 5.4) (Note 25).

2. Notes

1. Magnesium turnings were purchased from Aldrich Chemical Company, Inc.
2. Bromobenzene was purchased from Fisher Scientific and used without further purification.
3. A small amount of 1,2-dibromoethane was used to initiate the reaction.
4. An ice bath was used to control the reaction temperature during Grignard formation.
5. Copper(I) chloride was purified via the procedure in *Inorganic Syntheses*.³
6. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc. and used without further purification.
7. The organic layer was washed until the aqueous layer no longer turned blue.
8. The spectral properties of the product are as follows: ¹H NMR (300 MHz) δ : 1.25-1.53 (bm, 4 H), 1.62 (s, 1 H), 1.76 (m, 1 H), 1.84 (m, 2 H), 2.11 (m, 1 H), 2.42 (ddd, 1 H, J = 16.5, 10.8, 5.4), 3.64 (ddd, 1 H, J = 10.8, 10.8, 5.4) 7.17-7.35 (m, 5 H); ¹³C NMR (90 MHz) δ : 25.1 (t), 26.1 (t), 33.5 (t), 34.7 (t), 53.0 (d), 74.0 (d), 126.4 (d), 127.9 (d), 128.4 (d), 143.8 (s); IR cm⁻¹: 3592, 3461, 2941, 2863, 1604, 1497, 1451; MS 176 (M⁺), 158, 143, 130, 117, 104, 91 (base).
9. Chloroacetyl chloride (99%) was purchased from Fluka and used without further purification.
10. 4-Dimethylaminopyridine was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

11. Rapid addition of the bicarbonate solution may result in uncontrollable foaming.

12. Excess chloroacetyl chloride was slowly hydrolyzed to chloroacetic acid which was neutralized.

13. A creased or Morton flask was preferable as the rate of hydrolysis of the chloroacetate increases with efficient agitation.

14. The pH controller used was a Horizon Model 5997 available from Cole-Parmer Instrument Co.

15. A 250-mL graduated cylinder, used as a reservoir, was capped with a septum through which base-stable, 1/32"-I.D. tubing was run and connected to a peristaltic pump.

16. Fisher pH 7 buffer was used from the bottle as purchased.

17. Traces of chloroacetyl chloride are hydrolyzed to produce chloroacetic acid, producing a fluctuation in pH that will settle down within 5 min.

18. The lipase used was isolated from *Pseudomonas fluorescens* and was commercially available from Amano International Enzyme Co., Inc. (Troy, VA) as a powder, specific activity 32,000 units/g (P-30).

19. The rate enhancement was manifested by a more rapid base uptake.

20. If the hydrolysis was allowed to proceed, small additions of base (0.1 mL or less) occurred every 30 min or so.

21. If the hydrolysis was taken to 50% completion, the theoretical yield of each alcohol isomer was 36.96 g.

22. The (-)-(1R,2S) alcohol had an enantiomeric ratio of (-):(+) 99.2:0.8 corresponding to an enantiomeric excess (ee) of 98.4%. This determination resulted from GC analysis (50 m x 0.25 mm capillary column, OV-17 on fused silica, 250°C) of the α -methoxy- α -trifluoromethylphenylacetate (MTPA ester). The checkers determined the enantiomeric ratio to be 98.6:1.4 (97.2% ee) by ^1H NMR analysis at

300 MHz of the MTPA ester that was prepared as follows: The sample alcohol (0.1 mmol) was placed in a vial along with a solution of (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (0.15 mmol) in 1 mL of dichloromethane, triethylamine (0.15 mmol), and a crystal of 4-dimethylaminopyridine, and stirred at room temperature overnight. The excess acid chloride was treated with dimethylaminopropylamine (0.1 mmol). The MTPA ester was isolated in pure form after passing the mixture through a 5-g plug of silica gel and elution with 4:1 hexanes:ethyl acetate.

23. The silica gel used was 70-230 mesh as purchased from E. Merck.

24. TLC was run on 10 x 20-mm silica plates (E. Merck): TLC solvent was 4:1 hexanes:ethyl acetate; visualization was with 5% $(\text{NH}_4)_2\text{MoO}_4$ in 10% aqueous sulfuric acid, with heat. In the event that any mixed fractions are obtained, these are combined, evaporated, and the residue is rechromatographed in the same manner.

25. By GC analysis of (+)-MTPA esters (see Note 22), an enantiomeric ratio of (+):(-) 96.5:3.5, corresponding to 93% ee, was determined.

3. Discussion

The use of chiral auxiliaries to impart dissymmetry has become a powerful tool for controlling the stereochemical outcome of chemical transformations. Many of these auxiliaries have been drawn from the chiral pool of natural materials. While high levels of asymmetric induction have been achieved in many cases, none of these natural products has emerged as a general agent, in part because typically only one enantiomer of the auxiliary is readily available.

The procedure described here provides ready access to both the (+)- and (-) antipodes of trans-2-phenylcyclohexanol, a useful chiral auxiliary in ene reactions of its glyoxylate ester⁴ and its N-sulfinylcarbamate,⁵ as well as in cycloaddition reactions

of dienes with the N-sulfinylcarbamate,⁶ and olefins with ketenes.⁷ This simple auxiliary appears to retain⁴ many of the features of 8-phenylmenthol,⁸ a powerful agent difficult to prepare on a large scale.⁹ A modest-scale procedure for 8-phenylmenthol has appeared in *Organic Syntheses*.¹⁰

Optically pure trans-2-phenylcyclohexanol can also be prepared by resolution of the phthalate esters using brucine to obtain the (+)-alcohol and strychnine to obtain the (-)-alcohol (after basic hydrolysis of their respective salts).¹¹ Enzyme-catalyzed kinetic resolution of the acetate esters using pig liver esterase⁴ and pig liver acetone powder¹² has been used to prepare both enantiomers of this chiral auxiliary. The hydroboration of 1-phenylcyclohexene with isopinocampheylborane has been reported to give the chiral auxiliary in 97% enantiomeric excess.¹³

Racemic trans-2-phenylcyclohexanol has previously been prepared in a yield comparable to that realized in this procedure via copper-catalyzed phenyl Grignard addition to cyclohexene oxide using the more expensive copper(I) oxide.¹⁴

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(-)-(1R,2S)-trans-2-Phenylcyclohexanol: Cyclohexanol, 2-phenyl-, (1R-trans)- (11); (98919-68-7)

(+)-(1S,2R)-trans-2-Phenylcyclohexanol: Cyclohexanol, 2-phenyl-, (1S-trans)- (9); (34281-92-0)

Racemic trans-2-Phenylcyclohexanol: Cyclohexanol, 2-phenyl-, trans-(+)- (9); (40960-69-8)

Bromobenzene: Benzene, bromo- (8,9); (108-86-1)

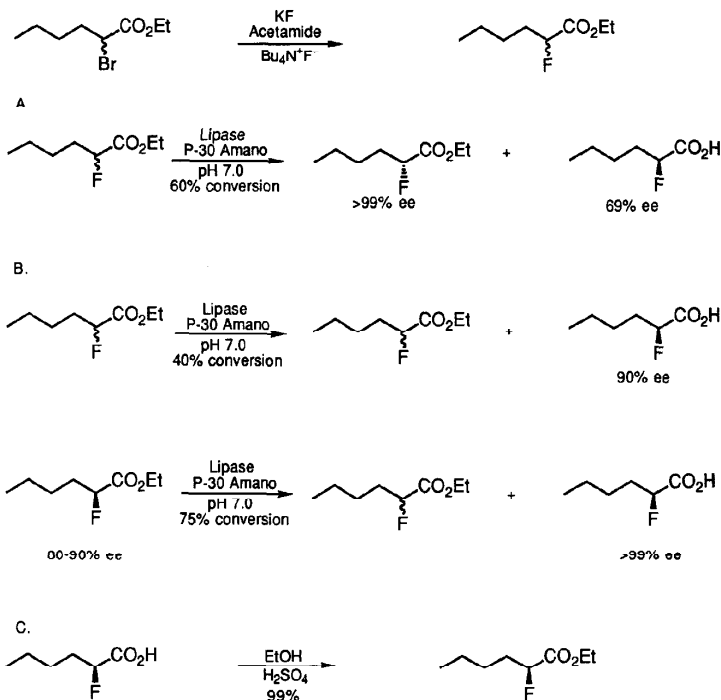
Cyclohexene oxide: 7-Oxabicyclo[4.1.0]heptane (8,9); (286-20-4)

Chloroacetyl chloride: Acetyl chloride, chloro- (8,9); (79-04-9)

4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

Lipase (*Pseudomonas fluorescens*): Lipase, triacylglycerol (9); (9001-62-1)

**ENANTIOMERICALLY PURE ETHYL (R)- AND (S)-
2-FLUOROHEXOANOATE BY ENZYME-CATALYZED KINETIC RESOLUTION
(Hexanoic acid, 2-fluoro-, ethyl ester, (R)- and (S)-)**



Submitted by P. Kararitis and R. W. Regenye.¹

Checked by Ronan Guevel and Leo A. Paquette.

1. Procedure

Ethyl 2-fluorohexanoate (Note 1). A 1-L flask equipped with a mechanical stirrer, thermometer, condenser and a gas adapter is charged under an atmosphere of argon with 38.5 g of acetamide and 80 g (0.36 mol) of ethyl 2-bromohexanoate (Note 2). The mixture is heated to 80°C until solution is effected and 38.6 g (0.65 mol) of potassium fluoride (Note 3) is added to it followed by 2.7 mL of tetra-n-butylammonium fluoride (Note 4). The resulting mixture is heated at 140°C with fast stirring for 4-5 hr (Note 5). The reaction mixture is allowed to cool to 90°C and then it is poured into 600 mL of ice. The reaction flask is rinsed with 100 mL of water and 100 mL of dichloromethane, which are added to the ice mixture. The aqueous phase is extracted with dichloromethane (4 x 200 mL). The combined organic layers are dried over anhydrous sodium sulfate and filtered. The dichloromethane solution is then cooled to 5°C and treated under an atmosphere of argon with 15 mL of bromine (Note 6). The reaction is judged complete after ~ 3 hr. It is quenched by adding 200 mL of saturated sodium thiosulfate solution. The two phases are separated and the organic phase is successively partitioned with saturated aqueous sodium bicarbonate solution (2 x 150 mL) and then with 200 mL of brine. It is finally dried over anhydrous sodium sulfate and concentrated to an oil at 40°C/7 mm (Note 7). Vacuum distillation at 36-37°C/0.8-0.9 mm affords 26.2-31.4 g (45-54% yield) of pure ethyl 2-fluorohexanoate as a colorless liquid (Note 8).

Method A. Enantiomerically pure ethyl (R)-2-fluorohexanoate (60% hydrolysis).

A 1-L Morton flask equipped with a mechanical stirrer, glass baffle, an electrode connected to a pH control unit and an addition tube connected to a syringe pump, is charged with 300 mL of 0.05 M aqueous phosphate buffer (pH 7.0) (Fisher), 300 mL of deionized water, and 70 g (0.43 mol) of ethyl 2-fluorohexanoate. The resulting mixture is stirred for several minutes and the pH is adjusted to 7.0 with the addition of a few

drops of 0.1 N sodium hydroxide solution. Then 0.43 g of *Pseudomonas* lipase enzyme (P-30, Amano International Enzyme Co., Inc., Troy, Virginia) is added and the hydrolysis is allowed to proceed at 5°C with stirring (reaction time ca. 2 hr). The pH is kept constant at 7.0 by adding 1.0 N sodium hydroxide solution via the syringe pump, which is activated by the pH control unit. The hydrolysis is discontinued when 260 mL of 1.0 N sodium hydroxide solution has been added (60% conversion, Note 9). The mixture is extracted with diethyl ether (5 x 300 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered, and concentrated at 40°C/70 mm. Vacuum distillation at 36-38°C/0.7-0.8 mm gives 24.0 g (34% yield, 85% of theory, Note 10) of pure ethyl (R)-2-fluorohexanoate, which is 97.5-99% enantiomerically pure, $[\alpha]_D^{25} +13.0$ to $+13.2^\circ$ (CHCl_3 , c 1.3) (Note 9). The aqueous layer is acidified to pH 2 with 3 N hydrochloric acid and extracted with diethyl ether (3 x 500 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered and concentrated at 40°C/70 mm. The residue is distilled at 71-72°C/0.7 mm to give 30.9 g (53% yield; 89% of theory) of (S)-2-fluorohexanoic acid, which is 53-68% enantiomerically pure (Note 11) $[\alpha]_D^{25} -6.8$ to -8.7° (CHCl_3 , c 1.3).

Method B. Enantiomerically pure ethyl (S)-2-fluorohexanoate. A 1-L, three-necked flask equipped with a mechanical stirrer, glass baffle, an electrode connected to a pH control unit and an addition tube connected to a syringe pump is charged with 300 mL of deionized water, 300 mL of 0.05 M phosphate buffer (pH 7.0) (Fisher), and 80 g (0.49 mol) of racemic ethyl 2-fluorohexanoate. The pH is adjusted to 7.0 with a few drops of 1 N aqueous sodium hydroxide solution, and 23 mg of *Pseudomonas* lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5-10°C with stirring. The pH is maintained at 7.0 by adding adequate 1 N aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 197 mL (40% conversion) of 1 N aqueous sodium hydroxide solution has been added (total reaction time: 2.5 hr). The reaction mixture

is immediately transferred to an extractor containing 750 mL of ethyl ether. The mixture is agitated for 5 min and the two phases are separated. The aqueous phase is extracted with ethyl ether (3 x 400 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered and concentrated at 30°C/70 mm to afford 47.2 g (98% of theory) of optically active ethyl (R)-2-fluorohexanoate. The aqueous phase is transferred back into the extractor and carefully acidified to pH 2.0 with concd hydrochloric acid. It is subsequently extracted with diethyl ether (4 x 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 30°C/70 mm to provide 26.1 g (39% yield; 98% of theory) of (S)-2-fluorohexanoic acid (81-86% ee).

Optical purity enhancement: A 1-L, three-necked flask equipped as described above is charged with 28.4 g (0.175 mol) of ethyl (S)-2-fluorohexanoate (81% ee) (Note 12), 300 mL of deionized water and 300 mL of 0.05 M phosphate buffer (pH 7.0). The pH is adjusted to 7.0 with a few drops of 1 N aqueous sodium hydroxide solution and 36 mg of *Pseudomonas* lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5°C. The pH is kept at 7.0 by adding adequate 1 N aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 131.3 mL (75% conversion) of 1 N aqueous sodium hydroxide solution has been added (total reaction time: 4 hr). The mixture is quickly extracted with ethyl ether (3 x 500 mL). The combined organic layers are dried over anhydrous potassium carbonate and concentrated at 35°C/70 mm to provide 5.66 g of nearly racemic ethyl 2-fluorohexanoate. The aqueous phase is acidified to pH 2.0 with concd hydrochloric acid and extracted with ethyl ether (4 x 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 35°C/70 mm to give 16.8 g (71% yield; 95.5% of theory) of (S)-2-fluorohexanoic acid. This acid is distilled at 67°C/0.4-0.5 mm to give 14.2 g of enantiomerically pure (S)-2-fluorohexanoic acid as a colorless oil: $[\alpha]_D^{25} -13.8^\circ$ (CHCl₃, c 1.7) (Notes 11 and 13).

Method C. Esterification of (S)-2-fluorohexanoic acid. A 250-mL flask is charged with 13.8 g of (S)-2-fluorohexanoic acid, 200 mL of ethanol and 2 mL of concd sulfuric acid. The solution is heated at reflux for 4 hr. Most of the ethanol is distilled slowly at atmospheric pressure and the residue is dissolved in 200 mL of dichloromethane after allowing it to cool to 23°C. The solution is partitioned with 200 mL of saturated aqueous sodium bicarbonate solution and the aqueous layer is back-extracted with 100 mL of dichloromethane. The combined organic layers are washed with 100 mL of brine, dried over anhydrous potassium carbonate and concentrated at 30°C/70 mm to afford 15.6 g (93% yield) of enantiomerically pure (Note 11) ethyl (S)-2-fluorohexanoate as a colorless liquid: $[\alpha]_D^{25} -13.8^\circ$ (CHCl₃, c 1.0). chemical purity 100% (GC analysis).

2. Notes

1. This procedure was originally used by P. Rosen, G. Holland and R. J. Karasiewicz at Hoffmann-La Roche. A similar procedure has appeared in the literature.²

2. Ethyl 2-bromohexanoate was purchased from Aldrich Chemical Company, Inc.

3. Potassium fluoride was purchased from Fluka and was ground to a fine powder prior to use.

4. Tetra-n-butylammonium fluoride was purchased from Aldrich Chemical Company, Inc.

5. The progress of the reaction was monitored by gas chromatography on an OV-17 column at 100-250°C (20°/min).

6. Bromine was added dropwise keeping the temperature below 10°C at all times. The progress of the reaction was monitored by gas chromatography as

described in Note 4. Bromine was added to brominate the α,β -unsaturated ester that was present as a by-product in the crude material. This procedure simplified the isolation of the ethyl 2-fluorohexanoate by distillation.

7. Some yellow solids appeared upon removing the solvent; they were filtered prior to distillation.

8. The purity of ethyl 2-fluorohexanoate was determined by gas chromatography as described above. The reaction yield varied from 42-70%.

9. % Conversion is based on the amount of base added.

10. % of the theoretical yield is based on the % of conversion.

11. The enantiomeric excess (% ee) of these compounds was determined by the submitters as follows. The ester and acids were first reduced to the corresponding alcohols with DIBAL and LAH, respectively. The alcohols were then allowed to react with 100% excess of (S)-(+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (Mosher's reagent) in (1:1) pyridine-carbon tetrachloride for 18 hr. The diastereomeric ratio of these derivatives was finally determined by Isothermal gas chromatography on a capillary OV-17 column at 160°C.

12. This ester was prepared from the optically active (S)-2-fluorohexanoic acid isolated above, by the esterification method described in this procedure.

13. The checkers have noted that the 2-fluorohexanoic acid crystallizes when allowed to stand at room temperature. This material can be recrystallized from pentane at low temperature. The crystals liquify on standing in the open air at room temperature.

3. Discussion

In recent years there has been an increasing interest in the use of enzymes and microorganisms to produce optically active compounds either by means of a kinetic

resolution or by stereospecific chemical transformations (e.g., reductions, oxidations, epoxidations, hydroxylations, etc.).³ Hydrolases in general have been used to effect kinetic resolutions of racemic esters and alcohols via their corresponding esters.⁴ Lipases, a subclass of hydrolases, are commercially available and relatively inexpensive. As a result, they constitute a very attractive class of catalysts for effecting kinetic resolutions, some of which might be difficult by other means.

Lipase P-30 Amano (ex *Psudeomonas fluorescens*) has been found to be synthetically useful in catalyzing very effectively kinetic resolutions of both racemic alcohols and racemic acids via their corresponding esters. This property is not generally observed with other enzymes and, therefore, makes this particular enzyme of greater synthetic utility. The enzyme can tolerate high concentrations of substrates and their hydrolysis products. The rates of the hydrolyses have usually been fast and the enantiomeric excesses achieved high. In most cases, the hydrolyses have been carried out in water and in the absence of co-solvents. These resolutions can be easily accomplished in multi kilogram scale. A wide variety of substrates have been resolved enantioselectively with this lipase.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl (R)-2-fluorohexanoate: Hexanoic acid, 2-fluoro-, ethyl ester, (R)- (12);
(124439-29-8)

Ethyl (S)-2-fluorohexanoate: Hexanoic acid, 2-fluoro-, ethyl ester, (S)- (12);
(124439-31-2)

Ethyl 2-fluorohexanoate: Hexanoic acid, 2-fluoro-, ethyl ester (8,9);
(17841-31-5)

Acetamide (8,9); (60-35-5)

Ethyl 2-bromohexanoate: Hexanoic acid, 2-bromo-, ethyl ester, (\pm)- (10); (63927-44-6)

Potassium fluoride (8,9); (7789-23-3)

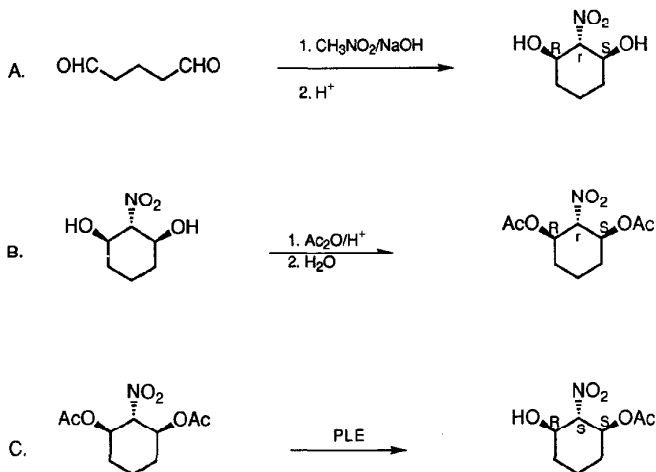
Tetrabutylammonium fluoride: Ammonium, tetrabutyl-, fluoride (8); 1-Butanaminium,
N,N,N-tributyl-, fluoride (9); (429-41-4)

(S)-2-Fluorohexanoic acid: Hexanoic acid, 2-fluoro-, (S)- (12); (113776-26-4)

ENANTIOSELECTIVE SAPONIFICATION WITH PIG LIVER ESTERASE

(PLE): (1S,2S,3R)-3-HYDROXY-2-NITROCYCLOHEXYL ACETATE

(1,3-Cyclohexanediol, 2-nitro-, 1-acetate, [1S-(1 α ,2 β ,3 α)])



Submitted by Martin Eberle, Martin Missbach, and Dieter Seebach.¹

Checked by David L. Coffen.

1. Procedure

A. *(1R,2r,3S)*-2-Nitrocyclohexane-1,3-diol. A 1-L, round-bottomed flask, equipped with a magnetic stirrer, a thermometer and an ice/ethanol bath is charged with 175 mL (0.455 mol) of an aqueous 25% solution of glutaric dialdehyde, 38 mL (0.708 mol) of nitromethane and 600 mL of methanol (Note 1). At 0-5°C 12 mL of aqueous 2 M sodium hydroxide is added gradually. The cooling bath is removed and

the reaction mixture is stirred for 4 hr at room temperature. The resulting yellow solution is neutralized by adding 15 g of acidic cation exchange resin and stirring for an additional 20 min (Note 2). The resin is filtered off and washed with a small volume of methanol. The filtrate is evaporated to a semi-solid residue using reduced pressure and a 35°C water bath. The residue is dissolved in 100 mL of absolute ethyl alcohol with heating and diluted by gradual addition of 250 mL of toluene. The resulting two-phase mixture (Note 3) is again evaporated, with azeotropic removal of water. The resulting residue is again taken up in 100 mL of hot ethyl alcohol and diluted with 250 mL of toluene (Note 3). The almost colorless crystals are filtered and dried at high vacuum to yield 44-52 g (60-70%) of nitrodiol, mp 152-155°C (dec.).

B. (1R,2r,3S)-3-Acetoxy-2-nitrocyclohexyl acetate. In a 1-L flask 52 g (0.323 mol) of the nitrodiol are suspended in 150 mL of acetic anhydride. Without cooling, 3-6 drops of concentrated sulfuric acid are added (Note 4). After 1 hr 500 mL of ice/water is rapidly added and stirring is continued for 60 min. The resulting colorless crystals are filtered, washed with water and air dried. The product thus obtained, 75.6 g (95.6%) of colorless crystals, is pure by TLC (4:1 hexane/ethyl acetate) and NMR, and melts at 89-90°C (Note 5).

C. (1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl acetate. A 500-mL flask equipped with a magnetic stirrer is charged with 10 g (41 mmol) of powdered nitrodiacetate and 300 mL of 0.2 M phosphate buffer of pH 7.0 prepared by dissolving 11 g of potassium dihydrogenphosphate and 3.3 g of potassium hydroxide in 300 mL of deionized (or distilled) water. To the stirred suspension is added 30 mg of purified PLE [Esterase (EC 3.1.1.1), suspended in 2.8 mL of 3.2 M ammonium sulfate buffer] (Note 6) and the mixture is stirred for 24 to 48 hr (Note 7). The continuously-measured pH drops to about 5.6 during the reaction and then remains almost constant, while the mixture has turned to a practically clear, pale yellow solution (Note 8). The solution is filtered through a paper filter and the filtrate is extracted three times with 100 mL of ether. The

organic phase is dried over anhydrous magnesium sulfate and filtered. Removal of the solvent and of the acetic acid under reduced pressure leaves 7-8 g (85-95%) of colorless monoacetate as a crystalline solid (Note 9). Recrystallization by dissolving in 100 mL of ether and adding 250 mL of pentane gives 5-6 g (60-70%) of pure (1S,2S,3R)-3-hydroxy-2-nitrocyclohexyl acetate (Note 10), mp 90-91°C, $[\alpha]_D +9.5^\circ$ (CHCl₃, c 1.0) (Note 11). From the mother liquor, another 1-2 g (12-24%) of monoacetate, mp 89-90°C, can be obtained (Note 12).

2 Notes

1. Commercial grade chemicals were used without further purification. The glutaric dialdehyde solution should be fresh.

2. The checkers used Amberlite IR-120(plus) acid form, capacity 1.9 meg/mL supplied by the Aldrich Chemical Company, Inc.

3. Two layers will form unless the water content of the crude product is sufficiently reduced during the preceding evaporation; in that case, the evaporation is to be repeated.

4. The solution turns clear and the temperature rises to 60-70°C when the reaction has started. More sulfuric acid should be added if a sustained exotherm does not ensue.

5. The submitters recommend recrystallization from alcohol/water (2:1). This is essential if NMR and TLC analyses of the crude nitrodiacetate indicate the presence of monoacetate.

6. The checker used the contents of one 30-mg vial of Sigma material, rinsed in with ca. 1 mL of deionized water. The submitters originally developed the process with PLE purified according to a procedure they had published previously.²

7. The submitters used 45 mg of enzyme and observed the reaction to be complete in 11.5 to 12.5 hr.

8. In addition to the monoacetate, a small amount of diacetate and an even smaller amount of diol could be detected by TLC in the crude product.

9. The crude product is enantiomerically pure according to ^{19}F -NMR of the corresponding Mosher ester (>97% ee). The checker observed lower $[\alpha]_{\text{D}}^{25}$ values (+8.72° and +8.61°) but confirmed the enantiomeric purity by HPLC analysis of the corresponding Mosher esters. By HPLC comparison with the diastereomeric mixture of Mosher esters prepared from a sample of racemic monoacetate (oily substance obtained by partial hydrolysis of diacetate) the (-)-enantiomer content appears to be less than 1%.

10. The absolute configuration of the product has been proved by X-ray analysis of the corresponding camphanic ester.^{2,3}

11. The monoacetate shows the following ^1H NMR spectrum (90 MHz) δ : 1.3-1.9 (m, 4 H), 2.0 (s, 3 H), 2.1-2.2 (m, 2 H), 2.7 (d, $J = 5.5$, OH), 4.1 (m, 1 H), 4.4 (apparent, t, $J = 10.5$, 1 H), 5.1-5.3 (m, 1 H).

12. Recrystallization of this fraction gave another 0.75-1.5 g (10-18%) of pure product.

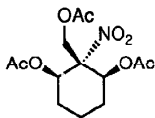
3. Discussion

The use of ester-cleaving enzymes is probably going to be one of the most useful biological-chemical methods in the synthetic laboratory. No example of this type of reaction has hitherto been published in the *Organic Syntheses* series of procedures. So far, the only biological-chemical *Organic Syntheses*-procedures are two yeast reductions,^{4,5} one oxidation with horse-liver-alcohol-dehydrogenase,⁶ and a disaccharide synthesis catalyzed by emulsin.⁷ The procedure described here is

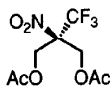
also applicable with crude enzyme powder, but the work-up is a bit more complicated, because a continuous extractor must be used to overcome problems with emulsions. Both crude enzyme concentrate and purified PLE as a mixture of Isoenzymes⁹ are commercially available, but the crude concentrate can easily be prepared from fresh pig liver and is thus very cheap.² By using self-made PLE-powder, the submitters have produced amounts of 20-25 g of pure monoacetate per run.²

Several review articles containing discussions of enantioselective syntheses with ester-cleaving enzymes have appeared recently (as of 1987).⁹⁻¹³ Of the many examples, the ones in which meso-substrates are employed are most attractive since the theoretical yield is 100%. In many applications of PLE the enantiomeric excess (% ee) of the product depends crucially upon the source of the enzyme. This effect has not been noticed in the enantioselective saponifications of nitrodiol diacetates, either because the reaction is insensitive to it, or because this complication is overcome by the great crystallization tendency of the products. The only problem we observed when the reaction was carried out with commercial crude PLE-powder (but not with the self made one) was the production of a certain amount of diol which could not be removed by simple recrystallization. In this case, filtration over a short silica gel column with methylene chloride as eluent gives after recrystallization pure monoacetate.

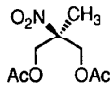
Other examples of enantiomerically pure monoacetates of meso-nitrodiols, which are available using the above procedure, are collected in Table 1. Entries 1 and 3 in Table 1 refer to runs following the above procedure, for all other cases the self made crude PLE-powder was used. Cases in which no reaction (a) or unsatisfactory selectivities (b) were observed, are shown below:



(a)



(a)

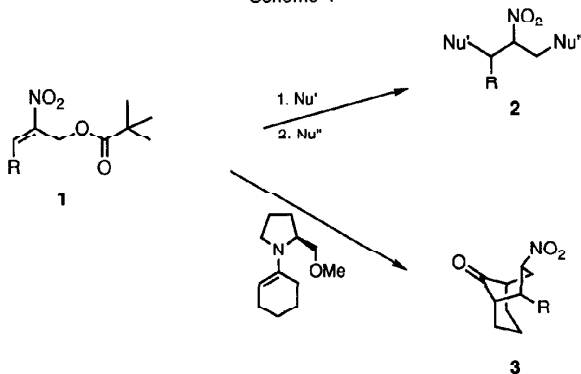


(b)

The meso-nitrodiol starting materials for the preparation of the PLE diacetate substrates are readily obtained from nitromethane or nitroethane and aldehydes or dialdehydes. They crystallize readily. The above procedures for the preparation of nitrocyclohexanediol and its diacetate from glutaraldehyde and nitromethane are modifications of published methods (Lichtenthaler,¹⁴ Baer¹⁵).

The chiral monoacetates now available are useful multiple coupling reagents¹⁶⁻¹⁸ for syntheses of enantiomerically pure target molecules. They can be converted to nitroolefinic allylic esters, achiral or racemic analogues of which we have previously shown¹⁶⁻¹⁸ to combine sequentially with two (different) nucleophiles (see 1-2 in Scheme 1).

Scheme 1



In a first approach to an enantioselective version of this method, we employed¹⁹ chiral enamines derived from proline.²⁰ (see 1-3 in Scheme 1). In this stoichiometric, enantioselective reaction, the valuable auxiliary used has to be recovered (i.e., recycled) in preparative-scale applications.²¹

We then used²² nitroallylic pivalates for the alkylation of hydroxy acid-derived enolates to prepare enantiomerically pure compounds (EPC), (see 4-5 in Scheme 2), an example of the use of the pool of chiral building blocks for EPC syntheses.²³⁻²⁵ Finally, the procedure described here allows for syntheses of EPC with a catalytic enantioselective step²⁶: dehydration of the monoacetate from the PLE saponification leads to (S)-nitrocyclohexenyl acetate **6**, and pivaloylation followed by acetate hydrolysis and dehydration leads to the pivalate **8** of the enantiomeric alcohol. These compounds can be used for substitutions with a variety of nucleophiles.^{2,3,26} Thus, starting from the enantiomerically pure Michael acceptors **6** and **8**, 3-alkyl nitrocyclohexenes **7** and **9**, respectively, of high enantiomeric excess are available (see Scheme 2, Nu = methyl lithium, phenyllithium and the morpholinoenamine of acetophenone):

Scheme 2

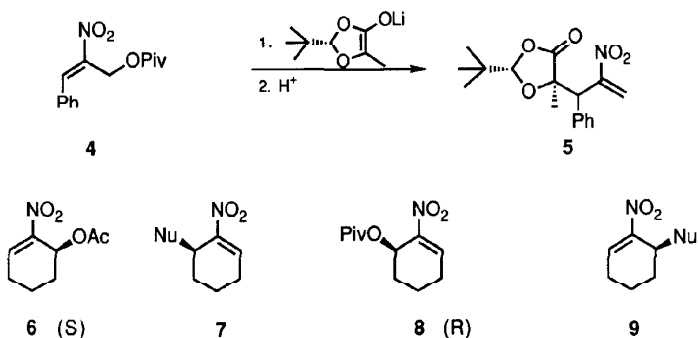
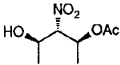
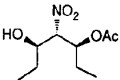
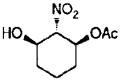
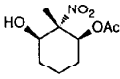
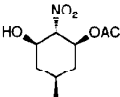
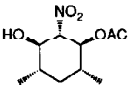
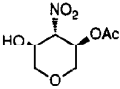
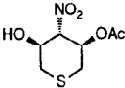
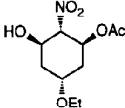


TABLE I

Yields, melting points, and specific rotations of nitrodiol monoacetates which were prepared by procedure C described above by using PLE-powder² instead of purified enzyme. Entries 1 and 3 in Table 1 refer to runs following the above procedure, for all other cases the self made crude PLE-powder was used. The configuration and the sense of chirality of the products of entries 1,3 and 4 were determined by x-ray crystal structure analysis of the camphanic esters, those of the other are inferred by analogy and by NMH comparison. The open chain compounds (entries 1 and 2) were obtained using TES buffer at pH 6.5

Entry No.		Yield [%]	Mp [°C]	$[\alpha]_D$ (CHCl ₃ , c 1)
1		50-70	58-60	-10.5
2		40-50	oil	-10.7
3		60-70	90-91	+ 9.8
4		80-90	106-107	-9.4
5		70-80	91-92	+29.1

6		60-70	130-131	-1.3
7		20-30	111-112	+14.7
8		60-70	130-131 (dec)	+28.1
9		60-70	93-94	+6.0

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl acetate: 1,3-Cyclohexanediol, 2-nitro-, 1-acetate. [1S-(1 α ,2 β ,3 α)]- (12); (108186-61-4)

(1R,2r,3S)-2-Nitrocyclohexane-1,3-diol: 1,3-Cyclohexanediol, 2-nitro-, (1 α ,2 β ,3 α)- (9); (38150-01-5)

Glutaric dialdehyde: Glutaraldehyde (8); Pentanedial (9); (111-30-8)

Nitromethane: Methane, nitro- (8,9); (75-52-5)

Amberlite IR-120(plus) acid form: Amberlite IR 120 Plus (10); (78922-04-0)

(1R,2r,3S)-3-Acetoxy-2-nitrocyclohexyl acetate: 1,3-Cyclohexanediol, 2-nitro-, diacetate (ester), (1 α ,2 β ,3 α)- (9); (51269-14-8)

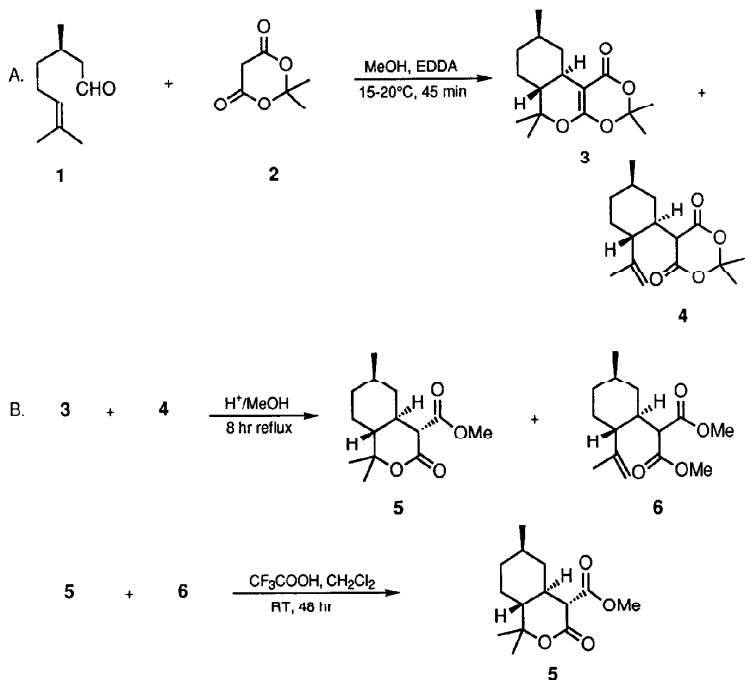
Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

**DIASTEREOSELECTIVE FORMATION OF α -METHOXYCARBONYL
LACTONES THROUGH AN INTRAMOLECULAR DIELS-ALDER REACTION:**

(4RS,4aRS,6RS,8aRS)-, (4S,4aS,6S,8aS)- AND (4R,4aR,6R,8aR)-

4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a-

OCTAHYDRO-2,3-BENZOPYRONE [rac-5, (+)-5, and (-)-5]



Submitted by L. F. Tietze, G. v. Kiedrowski, K.-G. Fahlbusch, and E. Voss.¹

Checked by Charles F. Marth and Edwin Vedejs.

1. Procedure

A. Diels-Alder-adduct rac-3.² A 250-mL round-bottomed flask equipped with a pressure equalizing addition funnel with a calcium sulfate-filled drying tube, a nitrogen inlet, and a magnetic stirring bar is charged with 2,2-dimethyl-1,3-dioxane-4,6-dione **2** (Meldrum's acid) (Note 1, 10.0 g, 69.4 mmol), a catalytic amount of ethylenediammonium diacetate (EDDA) (Note 2, 500 mg, 2.77 mmol) and dry methanol (150 mL). (R,S)-Citronellal (rac-1, Sigma; dried over MgSO_4 and distilled) (Note 3, 9.74 g = 11.4 mL, 63.1 mmol) is added under nitrogen (Note 4) over 15 min through the dropping funnel to the well-stirred mixture while the temperature is kept at 15-20°C by cooling the flask with a water bath. The solution is stirred for an additional 45 min at room temperature, the solvent is removed on a rotary evaporator (25°C), and the remaining yellow oil is dissolved in diethyl ether (300 mL). The organic layer is washed with water (50 mL), saturated sodium bicarbonate (2 x 50 mL), and brine (50 mL), and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gives an 8:1-mixture (16.5 g) of the Diels-Alder adduct rac-3 and the ene-product rac-4 as a yellow oil (Note 5).

B. Lactone 5. The crude mixture of rac-3 and rac-4 is dissolved in 300 mL of dry methanol (distilled from sodium) containing 10 drops of concd hydrochloric acid and heated under reflux for about 8 hr until the reactants can no longer be detected by thin layer chromatography (Note 6). The solvent is removed on a rotary evaporator at 25°C and the remaining residue, which consists of an 8:1 mixture of lactone rac-5 and dimethyl ester rac-6 is dissolved in dry dichloromethane (50 mL). The solution is acidified with trifluoroacetic acid (10 mL) and stirred at room temperature for about 48 hr, until the thin layer chromatogram does not show any dimethyl ester rac-6 (Note 6). The organic layer is washed with water (50 mL), saturated sodium bicarbonate solution (2 x 50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate,

filtered, and concentrated on a rotary evaporator. Distillation of the remaining thick, yellow oil under reduced pressure in a short path distillation apparatus with an aircooled condenser gives 12.6 g (79%) of rac-5, bp 133-135°C/0.001 mm. The colorless oil is dissolved in tert-butyl methyl ether (10 mL) and hexane (80 mL) and the solvent is allowed to evaporate over 2 days to about 15% of the original volume. Lactone rac-5 (8.11 g, 53%) slowly crystallizes (mp 69-71°C) (Notes 7, 8). If the above procedure is repeated with the mother liquor, a variable additional amount of rac-5 (Note 8) is obtained.

With (S)-citronellal the (4S,4aS,6S,8aS)-lactone (+)-5 is obtained; with (R)-citronellal the (4R,4aR,6R,8aR)-lactone (-)-5 is obtained (Notes 3, 7).

2. Notes

1. Meldrum's acid is commercially available from Merck-Schuchardt, Fluka, or Aldrich Chemical Company, Inc., or it can be prepared by the reaction of malonic acid with acetone.³

2. Ethylenediammonium diacetate (EDDA) is prepared as follows.⁴ A 250-mL, round-bottomed flask with a stirring bar and a pressure equalizing addition funnel with a calcium sulfate-filled drying tube is charged with dry ethylenediamine (12.0 g, 0.20 mol) and dry ether (100 mL). Acetic acid (24.0 g, 0.40 mol) in dry ether (20 mL) is added through the dropping funnel to the stirred solution. The reaction mixture is left at 4°C for 14 hr and the crystals are collected by filtration and washed with ether. Recrystallization from methanol provides 19.8 g (83%) of pure EDDA, mp 114°C, as white needles; IR (KBr) cm^{-1} : 3500-2000 (NH), 2180 (MH₃⁺), 1650 (C=O), 1600-1400 (CO₂⁻); ¹H NMR (CDCl₃) δ : 1.90 (s, 6 H, CH₃), 3.20 (s, 4 H, CH₂), 5.75 (s, 6 H, NH₃⁺).

EDDA is the best catalyst for the condensation. Piperidine acetate gives side products.

3. (R,S)-Citronellal can be purchased from BASF, and (R)-citronellal from Dragoco, Fluka, or Takasago Perfumery Co., Ltd., Japan. (R)-Citronellal can also be synthesized from pulegone with ee >99%.⁵ (S)-Citronellal may be obtained by oxidation of (S)-citronellol,⁶ which is accessible by different routes with ee 95%.⁷ The optical purity of citronellal can be determined by GLC after conversion to the acetal of (-)-(2R,4R)-pentanediol.⁸ For the reactions described, (R,S)-citronellal from BASF, (R)-citronellal from Dragoco, and (S)-citronellol from Fluka were used. (R,S)-Citronellal and (S)-citronellal were distilled under nitrogen before use (bp 83-85°C/11 mm), (S)-citronellal: $[\alpha]_{\text{D}}^{20} -11.5^\circ$ (chloroform, c 0.1); (R)-citronellal ($[\alpha]_{\text{D}}^{20} +13 \pm 1^\circ$) and (S)-citronellol ($[\alpha]_{\text{D}}^{20} -4.9 \pm 0.2^\circ$) were used as purchased.

4. The reaction can also be performed without using inert gas, but the yields may be lower.

5. The pure Diels-Alder adduct **3** can be obtained by crystallization of the crude reaction product from ether/hexane: white needles, mp 104-106°C; IR (KBr) cm^{-1} : 2950, 2930, 2860 (C-H), 1715 (C=O), 1615 (C=C, 1400, 1265; ¹H NMR (CDCl_3) δ : 0.40 (m, 1 H, 4 β -H), 0.7-2.5 (m, 7 H, CH + CH₂), 0.90 (d, 3 H, J = 7, CH₃), 1.23, 1.43, 1.70, 1.73 (s, 3 H, CH₃), 2.75 (dt, 1 H, J₁ = 12, J₂ = 2, 4-H). When the pure Diels-Alder adduct **3** is heated in dry methanol under reflux for 3 hr, **5** (mp 68-70°C) is obtained in 92% yield from **3**.

6. Macherey-Nagel Polygram SIL G/UV₂₅₄-plates were used with 2:5 v/v ether/hexane as eluant. The Diels-Alder product **3** (R_f = 0.29), is visible under short wavelength ultraviolet light, whereas the detection of **4** (R_f = 0.33), rac-**5** (R_f = 0.22) and **6** (R_f = 0.47) is effected by development in an iodine chamber.

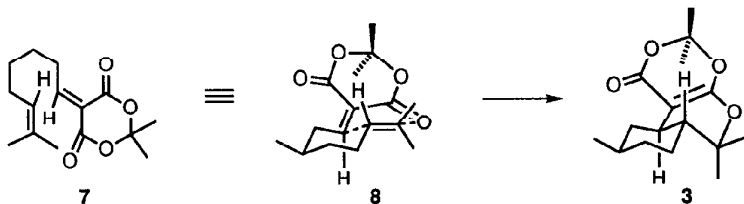
7. The physical properties of rac-**5**, (+)-**5**, and (-)-**5** are as follows: (+)-**5**, $[\alpha]_{\text{D}}^{20} +44.1^\circ$ (chloroform, c 1.004); (-)-**5**, $[\alpha]_{\text{D}}^{20} -44.0^\circ$, (chloroform, c 0.995); IR (KBr) cm^{-1} : 2980, 2950, 2930, 2870, (CH), 1745, 1725 (C=O), 1450, 1320; ¹H NMR (200 MHz, CDCl_3) δ : 0.74 (ddd, 1 H, J = 12, 12, 12, 5 β -H), 0.86-1.7 (m, 5 H, 6, 7 β , 8 α , 8 β -H).

0.95 (d, 3 H, $J = 6.5$, 6-CH₃), 1.36 (s, 3 H, 1 α -CH₃), 1.7-1.9 (m, 2 H, 5 α , 7 α -H), 1.42 (s, 3 H, 1 β -CH₃), 2.16 (dddd, 1 H, $J = 3.5, 12, 12, 12$, 4 α -H), 3.09 (d, 1 H, $J = 12$, 4-H), 3.81 (s, 3 H, OCH₃); ¹³C NMR (50.3 MHz, CDCl₃) δ : 22.0 (1 α -CH₃), 23.3 (6-CH₃), 27.2 (C-7), 28.2 (1 β -CH₃), 31.6 (C-6), 34.2 (C-8), 36.0 (C-8a), 40.5 (C-5), 45.9 (C-4a), 52.6 (OCH₃), 55.1 (C-4), 86.6 (C-1), 167.1 (C=O), 169.6 (C-3); MS (70 eV): $m/e = 254$ (1%, M⁺), 239 (6%, M-CH₃), 223 (2%, M-OCH₃), 196 (50%, M-C₃H₆O), 168 (15%, 106-CO), 109 (22%, 168-CO₂CH₃), 101 (100%), 59 (55%, CO₂CH₃).

8. Crystallization of the crude material without distillation from tert-butyl methyl ether/hexane affords 56% of rac-**5**, mp 68-70°C, as pale yellow crystals. The submitters obtained a second crop of 1.5 g from crystallization of distilled material; mp 68-78°C, starting from citronellal purchased from BASF. The checkers found that citronellal from Sigma required distillation and gave an impure second crop of **5** only with difficulty.

3. Discussion

Lactone **5** can be obtained in both enantiomeric forms or as a racemate according to the described procedure. The reaction sequence includes the in situ formation of an alkylidene-1,3-dicarbonyl system **7** which can act as a heterodiene in an intramolecular hetero-Diels-Alder addition. A small amount of the ene product **4** with de > 98% is formed at room temperature as well. The remarkable selectivity in formation of diastereomer **3** is explained by an energetically more favorable exo transition state **8** with a pseudo-chair arrangement having the methyl group quasi-equatorial. Polycyclic cis-fused compounds can also be synthesized by the procedure above,⁹ and a related sequence to the cannabinoid skeleton has been described using appropriate 1,3-dicarbonyl reactants.¹⁰



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,2-Dimethyl-1,3-Dioxane-4,6-dione (Meldrum's Acid): Malonic acid, cyclic isopropylidene ester (8); 1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

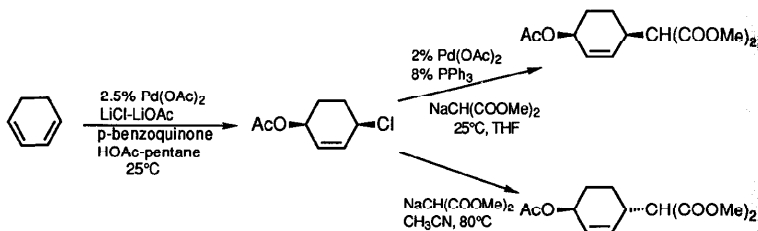
Ethylenediammonium diacetate: 1,2-Ethanediamine diacetate (9); (38734-69-9)

(R)-Citronellal: 6-Octenal, 3,7-dimethyl-, (R)-(+)- (8,9); (2385-77-5)

[6aR-(6a α ,9 α ,10a β)]-Octahydro-3,3,6,6,9-pentamethyl-1H,6H-[1,3]dioxino-[4,5-c][2]benzopyran-1-one: 1H,6H-[1,3]Dioxino[4,5-c][2]benzopyran-1-one, octahydro-3,3,6,6,9-pentamethyl-, [6aR-(6a α ,9 α ,10a β)]- (10); (78394-10-2)

**STEREoselective 1,4-FUNCTIONALIZATIONS OF CONJUGATED
DIENES: *cis*- and *trans*-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-
2-CYCLOHEXENE**

**(Propanedioic acid, [4-(acetyloxy)-2-cyclohexen-1-yl]-,
dimethyl ester, *cis*- and *trans*-)**



Submitted by Jan-E. Bäckvall and Jan O. Vågberg.¹

Checked by Michael R. Sestrick and Albert I. Meyers.

1. Procedure

A. *cis*-1-Acetoxy-4-chloro-2-cyclohexene. A 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 200 mL of acetic acid, 5.1 g (0.12 mol) of lithium chloride, 12.2 g (0.12 mol) of lithium acetate dihydrate, 0.67 g (3 mmol) of palladium acetate, and 12.9 g (0.12 mol) of p-benzoquinone. The contents of the flask are stirred at room temperature until all components are dissolved, and 300 mL of pentane is added. To the pentane phase of the biphasic system formed is added 4.82 g (60 mmol) of 1,3-cyclohexadiene (Note 1). The reaction mixture is stirred at a moderate rate (Note 2) at room temperature and after 4 hr, 2.87 g (33 mmol) of manganese dioxide (Note 3) is added. After the flask is stirred for another 4

hr at room temperature, the organic phase is separated and saved, and 2.87 g (33 mmol) of manganese dioxide and 20 mL of acetic acid are added to the remaining acetic acid, which is vigorously stirred for 30 min. To the mixture are added 2.6 g (60 mmol) of lithium chloride and 300 mL of pentane. A new portion of 4.82 g (60 mmol) of 1,3-cyclohexadiene is added and the reaction mixture is stirred at a moderate rate (Note 1) at room temperature overnight (12-15 hr). To the reaction mixture is added 70 mL of saturated sodium chloride solution and the organic phase is separated and saved. The aqueous phase is filtered and extracted with pentane (2 x 300 mL). The combined organic phases are washed with water (2 x 120 mL), 120 mL of saturated aqueous sodium carbonate, 120 mL of 2 M sodium hydroxide, 120 mL of water and 120 mL of saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and the solvent is removed by rotary evaporation at reduced pressure giving 16.5-17.5 g (79-84%) of a yellow oil. Kügelrohr distillation (95-105°C, 1 mm) of the crude product affords 14.6-15.6 g (71-75%) of pure *cis*-1-acetoxy-4-chloro-2-cyclohexene (> 98% *cis*). Analysis by HPLC and GLC shows about 1% contamination of diacetate as the only impurity. No dichloride can be detected (< 0.5%).

B. cis-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene. A 2-L, two-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen-vacuum inlet, and a rubber septum, is charged with 17.5 g (0.1 mol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene, 0.49 g (2.2 mol) of palladium acetate and 2.4 g (9.0 mmol) of triphenylphosphine (Note 4). The flask is flushed with nitrogen (Note 5). To the flask is added 550 mL of a 0.2 M solution (0.11 mol) of sodium dimethyl malonate in tetrahydrofuran (THF) by syringe (Note 6). The flask is again flushed with nitrogen and the reaction mixture, which now has turned yellow, is stirred at room temperature for 2 hr (Note 7). The flask is opened and 200 mL of saturated aqueous sodium bicarbonate is added. The stirring is continued for 20 min, and then 100 mL of water

and 200 mL of ether are added. The contents of the flask are transferred into a 2-L separatory funnel and the organic phase is separated. The remaining aqueous phase is extracted with ether (3 x 300 mL). The combined organic phases are washed with 200 mL of saturated brine, dried over anhydrous magnesium sulfate, concentrated on a rotary evaporator to approximately 400 mL, and then filtered through a short silica gel column (Note 8). Removal of the rest of the solvent by rotary evaporation at reduced pressure gives 30.4-31.3 g of a light brown oil. Excess dimethyl malonate is removed by Kügelrohr distillation at 100°C (1 mm). Kügelrohr distillation (140°C, 0.2 mm) of the remaining crude product affords 25.9-26.7 g (91%) of *cis*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a light brown oil. Analysis by GLC indicates a chemical purity of 95-98%.

C. trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene. In a 1-L, two-necked flask equipped with a reflux condenser, nitrogen gas inlet, and a magnetic stirring bar are placed 8.73 g (50 mmol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene and 400 mL of a 0.16 M solution (72 mmol) of sodium dimethyl malonate in acetonitrile (Note 9). The flask is flushed with nitrogen and then heated in an oil bath at reflux for 21 hr. The reaction mixture is cooled to room temperature and 5 g of solid sodium hydrogen carbonate is added. The mixture is stirred for 2 hr, poured into 800 mL of ether and the resulting mixture is filtered. The organic phase is collected and the solvent is removed on a rotary evaporator to afford 16.1 g of the product together with dimethyl malonate. The excess dimethyl malonate is removed by Kügelrohr distillation at 70°C (0.2 mm). The residual crude yellow oil was dissolved in a minimal amount of ethyl acetate and passed through a short silica plug (30-35 g, Alfa 53 micron silica), eluting with a small amount of fresh ethyl acetate. Removal of ethyl acetate on a rotary evaporator and further concentration at 0.2 mm overnight yielded 11.6-12.2 g (86-90%) of *trans*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a clear oil, essentially pure (99% by GLC) (Note 10).

2. Notes

1. 1,3-Cyclohexadiene was obtained from Aldrich Chemical Company, Inc. and distilled before use. It can also be synthesized according to *Org. Synth., Coll. Vol. V* 1973, 285.
2. A stirring rate of 5-10 rps was used (only a small vortex was present).
3. Commercial, active manganese dioxide from Merck-Schuchardt was used.
4. Palladium acetate and triphenylphosphine generate the active tri- or tetrakis(triphenylphosphine)palladium(0) catalyst on addition of sodium dimethyl malonate.
5. A manifold system connected to a vacuum line and a nitrogen line was used.
6. Sodium dimethyl malonate was prepared from equimolar amounts of sodium hydride and dimethyl malonate.
7. The reaction is usually over after 30 min. The reaction was checked by GLC or TLC to confirm completion.
8. This filtration was done in order to remove remaining palladium species and phosphine oxide. A column (4 x 8 cm) packed with Alfa Silica Gel (58 microns) was used.
9. Acetonitrile was stirred overnight with calcium hydride and then distilled onto freshly activated 4 Å molecular sieves.
10. All GLC analyses were performed on a 2.4-m x 6-mm glass column packed with 5% SE-30 on Chromosorb W or crosslinked 50% phenylmethylsilicone.

3. Discussion

This procedure for stereoselective 1,4-functionalization of 1,3-dienes is based on 1,4-acetoxychlorination,² and allows the preparation of 1,4-disubstituted 2-cyclohexenes with full stereocontrol of the carbon-carbon bond formation in the 4-position. It is also highly regioselective. Other procedures^{3,4} for obtaining 4-alkyl-substituted 3-cyclohexenol derivatives use 1,3-cyclohexadiene monoepoxide as starting material. None of the previous methods allow the selective preparation of both stereoisomers as shown here.

The present procedure uses palladium catalysis in the first step and in one of the second steps. These reactions occur under very mild conditions (room temperature) and the catalyst used is commercial palladium acetate.

Since the title compounds can be stereoselectively functionalized in the 1 position by metal-catalyzed nucleophilic substitutions of the acetoxyl group, a great number of 1,4-disubstituted 2-cyclohexenes with defined 1,4-relative stereochemistry are available.

While the process works for a great number of conjugated dienes, a few, such as 1,3-cyclopentadiene and those acyclic dienes that have an oxygen substituent in an allylic position, did not give a chloroacetoxylation product.^{2a} Control of the 1,4-relative stereochemistry and preparation of compounds analogous to the title compounds also work for acyclic dienes,^{2a,5} This process was used to obtain remote stereocontrol in acyclic systems and applied to the synthesis of a pheromone.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

cis-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene: Propanedioic acid,

[4-(acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, cis- (11); (82736-52-5)

trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene: Propanedioic acid,

[4-(acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, trans- (11); (82736-53-6)

cis-1-Acetoxy-4-chloro-2-cyclohexene: 2-Cyclohexen-1-ol, 4-chloro-, acetate,

cis- (11); (82736-39-8)

Lithium acetate dihydrate: Acetic acid, lithium salt, dihydrate (8,9); (6108-17-4)

Palladium acetate: Acetic acid, palladium(2+) salt (8,0); (3375-31-3)

p-Benzoquinone (8); 2,5-Cyclohexadiene-1,4-dione (9); (106-51-4)

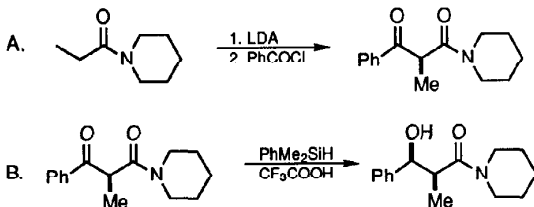
1,3-Cyclohexadiene (8,9); (592-57-4)

Manganese dioxide: Manganese oxide (8,9); (1313-13-9)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

ERYTHRO-DIRECTED REDUCTION OF A β -KETO AMIDE: ERYTHRO-1-(3-HYDROXY-2-METHYL-3-PHENYLPROPANOYL)PIPERIDINE
(Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R^*,R^*)-(±)-)



Submitted by M. Fujita and T. Hiyama.¹

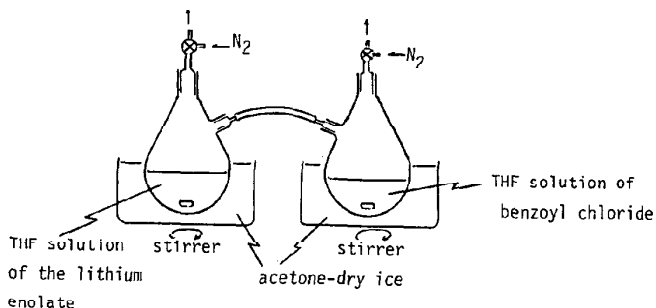
Checked by Gregory P. Roth and Albert I. Meyers.

1. Procedure

A. 1-(2-Benzoylpropionyl)piperidine. A dry, 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with nitrogen. One neck is connected to a three-way stopcock equipped with a balloon filled with nitrogen, and the other neck is capped with a rubber septum. The flask is charged with 100 mL of anhydrous tetrahydrofuran (THF) (Note 1) and 10.1 g (14.1 mL, 0.100 mol) of diisopropylamine (Note 2) and immersed in an acetone-dry ice bath. A 1.68-M hexane solution of butyllithium (60 mL, 0.10 mol) (Note 3) is added dropwise with stirring over a 10-min period, and the stirring is continued for 1 hr at -78°C . To the resulting lithium diisopropylamide (LDA) solution is added dropwise 14.1 g (0.100 mol) of propanoylpiperidine (Note 4) with stirring over a 10-min period, and the stirring is continued for 2 hr at -78°C (Note 5). The rubber septum is replaced with a polyvinyl chloride (or Teflon) tube connected to another 300-mL, two-necked, round-bottomed

flask, which is equipped with a magnetic stirrer and a three-way stopcock, charged with 100 mL of anhydrous THF and 13.5 g (16.3 mL, 0.110 mol) of benzoyl chloride (Note 6), and immersed in an acetone-dry ice bath. The balloon is taken off and nitrogen is passed through the two stopcocks so that the reaction mixture does not come in contact with air (see the apparatus shown in Figure 1). By inclining the first flask, the THF solution of the lithium enolate of 1-propanoylpiperidine is added to the THF solution of benzoyl chloride in the second flask through the polyvinyl chloride tube over a 5-min period. After the solution is stirred for 0.5 hr at -78°C , it is allowed to warm to room temperature, diluted with 200 mL of dichloromethane, and washed with 200 mL of water. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of diethyl ether. The combined organic layers are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. Recrystallization from diethyl ether-hexane affords 12.5 g (51%) of 1-(2-benzoylpropanoyl)piperidine, mp $100\text{--}101^{\circ}\text{C}$ (Note 7).

Figure 1



B. erythro-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine. A 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with nitrogen. One neck is connected with a balloon charged with nitrogen, and the other neck is capped with a rubber septum. Into the flask are placed 50 ml of trifluoroacetic acid (Note 8) and 11.9 g of 1-(2-benzoylpropanoyl)piperidine (48.7 mmol) prepared in Part A; then the flask is immersed in an ice-water bath. To the flask is added 7.3 g of dimethylphenylsilane (8.24 mL, 54 mmol) (Note 9) over a period of 5 min with the aid of a 10-mL syringe, and the resulting mixture is stirred for 4 hr in the ice bath. The mixture is diluted with 200 mL of dichloromethane and washed with 200 mL of water. After the organic layer is separated, the aqueous layer is extracted with two 50-mL portions of diethyl ether, and the combined organic layers are concentrated with a rotary evaporator (Note 10). The crude oil is placed in a 200-mL, one-necked flask and dissolved in 100 mL of methanolic 1 M sodium hydroxide. The solution is stirred for 1.5 hr at ambient temperature with a magnetic stirrer. The mixture is diluted with 200 mL of dichloromethane and washed with 50 mL of water. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of diethyl ether. The combined organic layers are dried over anhydrous magnesium sulfate and concentrated by rotary evaporation (Note 11). The residual oil is subjected to column chromatography using 100 g of silica gel (Note 12). After the first fraction (800 mL) of hexane is eluted, the second fraction, eluted with 500 mL of diethyl ether, is collected and concentrated. Recrystallization of the resulting oil from diethyl ether-hexane gives 10.2 g of material, mp 85-86°C. The yield is 90% (Note 13).

The analogous threo derivatives can be made by use of tris(diethylamino)sulfonium difluorotrimethylsilicate as the catalyst (Note 14).

2. Notes

1. Tetrahydrofuran (THF) is freshly distilled over benzophenone ketyl.
2. Diisopropylamine is distilled over calcium hydride.
3. The hexane solution of butyllithium is purchased from Wako Pure Chemicals Industries, LTD, and titrated before use.
4. Propanoylpiperidine is prepared from propanoyl chloride and piperidine according to a similar procedure described in ref. 2.
5. The lithium enolate of (2-benzoylpropanoyl)piperidine should be handled below -20°C , as it decomposes above 0°C .
6. Benzoyl chloride of commercial grade is distilled before use.
7. Spectral characteristics are as follows: ^1H NMR (CDCl_3) δ : 1.46 (d, 3 H, $J = 7.2$), 1.3-1.7 (m, 6 H), 3.25-3.65 (m, 4 H), 4.40 (q, 1 H, $J = 7.2$), 7.25-7.65 (m, 3 H), 7.85-8.05 (m, 2 H); IR (KBr) cm^{-1} : 1696, 1620, 1450, 1204, 686; MS (50 eV) m/z rel intensity) 245 (M^+ : 14), 140 (37), 105 (100), 84 (99), 77 (47). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 7.87; N, 5.69.
8. Trifluoroacetic acid was purchased from Aldrich Chemical Company, Inc. (also available from Tokyo Kasei Co. LTD, Japan), and used directly.
9. Dimethylphenylsilane was purchased from Aldrich Chemical Company, Inc. (also available from Shin-etsu Kagaku Co. LTD, Japan), and used directly.
10. About half of the product is trifluoroacetylated during the concentration procedure.
11. A 400-MHz ^1H NMR analysis of the crude oil showed exclusive formation of the erythro isomer of the material (>99:1).
12. A glass column (35 mm x 20 cm) packed with Wakogel C-200 is used.
13. Spectral characteristics are as follows: ^1H NMR (CDCl_3) δ : 1.03 (d, 3 H, $J = 7$), 1.3-1.7 (m, 6 H), 2.84 (dq, 1 H, $J = 2.5, 3$), 3.2-3.7 (m, 4 H), 4.30 (broad s, 1 H), 5.06

(d, 1 H, $J = 2.5$), 7.2-7.4 (m, 5 H); IR (KBr) cm^{-1} : 3350, 1606; MS (rel intensity) m/z , 247 (M^+ ; 7), 232 (20), 141 (100), 112 (26), 84 (43), 79 (20). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.74; H, 8.69; N, 5.52.

14. *threo*-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine. A 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with dry nitrogen. One neck is connected with a three-way stopcock, one arm of which is connected to a balloon filled with nitrogen. The other neck is capped with a rubber septum. The flask is evacuated with a vacuum pump under heating with a heat-gun and nitrogen is admitted. This operation is repeated three times to replace the inner atmosphere of the flask completely with dry nitrogen. In the flask are placed 50 mL of hexamethylphosphoric triamide (Note 15), 12.3 g of 1-(2-benzoylpropanoyl)piperidine (50 mmol), and 8.2 g of dimethylphenylsilane (9.2 mL, 60 mmol) by syringe, and then the flask is immersed in an ice-water bath. To the flask is added dropwise 2.5 mL of a 1 M tetrahydrofuran (THF) solution of tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) (2.5 mmol) (Note 16) with the aid of a syringe, and the resulting mixture is stirred for 6 hr at ice-bath temperature. In order to complete the reaction, 3.4 g of dimethylphenylsilane (3.8 mL, 25 mmol) and 1.5 mL of a 1-M THF solution of TASF (1.5 mmol) are added and stirring is continued for an additional 6 hr at the same temperature. The mixture is quenched with 50 mL of 1 M hydrochloric acid, stirred for 1.5 hr at ambient temperature, and extracted with three 100-mL portions of diethyl ether. The organic layer is washed with 50 mL of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The crude oil is subjected to column chromatography using 100 g of silica gel (Note 17). After the first fraction, eluted with 800 mL of hexane, is removed, the second fraction, eluted with 500 mL of diethyl ether, is concentrated (Note 18). Recrystallization of the residue from diethyl ether-hexane gives 8.03 g (65%) of material, mp 79-80°C (Note 19). The mother liquor is concentrated and again subjected to column chromatography (Note

20) to give the same material, which, after recrystallization from diethyl ether-hexane, melts at 77-79°C (1.5 g, 12%). The total yield amounts to 77%.

15. Hexamethylphosphoric triamide is distilled from calcium hydride under reduced pressure of nitrogen. In place of hexamethylphosphoric triamide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU), which is dried and purified similarly,⁷ can be used.

16. TASF was prepared according to the procedure of reference 3. Typically, diethylamino(trimethyl)silane (6.4 g, 8.3 mL, 44 mmol) is added drop by drop under a dry inert atmosphere to an ethereal solution (20 mL) of diethylaminosulfur trifluoride (DAST, purchased from Aldrich Chemical Company, Inc., and used directly) (3.2 g, 2.4 mL, 20 mmol) under cooling with a dry ice/acetone bath. The mixture is allowed to warm to room temperature and stirred for 72 hr at room temperature. The initial homogeneous solution separates into two layers. The upper layer is removed with the aid of a syringe. The lower layer is washed with dry ether (10 mL x 3) and dried under reduced pressure to afford TASF as a solid (6.0 g, 16.6 mmol, 83% yield). All the isolation operations should be carried out under an inert atmosphere such as nitrogen. The solid is dissolved in THF to give a 1-M solution (the volume of the solution is 16.6 mL) which is stored under a dry nitrogen atmosphere.

17. A glass column (35 mm x 20 cm) packed with Wakogel C-200 is used.

18. A 400-MHz ¹H NMR analysis of the crude oil showed exclusive formation of the threo isomer of the material (>99%).

19. Spectral characteristics are as follows: ¹H NMR (CDCl₃) δ: 1.22 (d, J = 7.3 H), 1.1-1.7 (m, 6 H), 2.8-3.8 (m, 5 H), 4.7-4.8 (m, 2 H), 7.31 (s, 5 H); IR (KBr) cm⁻¹: 3380, 1606; MS (rel intensity) m/z 247 (M⁺; 6), 232 (16), 141 (100), 112 (23), 84 (39), 79 (15). Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.70; H, 8.63; N, 5.65.

20. A glass column (20 mm x 25 cm) packed with 50 g of Wakogel C-200 is used. After the first fraction, eluted with 300 mL of dichloromethane, was removed, the second fraction, eluted with 300 mL of dichloromethane-diethyl ether (1:4), was concentrated.

3. Discussion

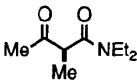
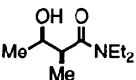
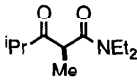
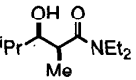
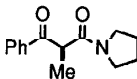
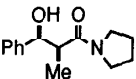
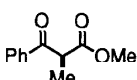
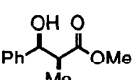
Aldols of the erythro configuration are prepared by aldol condensation of various metal enolates.⁴ An alternative approach is reduction of β -keto esters⁵ or amides⁶ with zinc borohydride. The hydrosilane-based reduction described here provides erythro aldols under high stereocontrol and is practical because of the mild conditions and easy handling of readily available hydrosilanes.⁷ The scope of this reduction is summarized in Table I. No epimerization at the chiral center is observed as shown in the last entry. The erythro-selective reduction with the $\text{PhMe}_2\text{SiH}/\text{CF}_3\text{COOH}$ reagent is also applicable to the reduction of 2-oxy or 2-amino ketones.^{8,9}

Preparation of threo aldols is sometimes a problem. For stereoselective synthesis by aldol condensation, propionate esters of mesitol must be employed.¹⁰ A general, alternative approach to threo aldols is threo directed reduction of β keto esters.¹¹ Although the stereoselectivity of this reduction is usually low, reduction of β -keto amides with potassium triethylborohydride (KBHET_3) is extremely selective.¹² The hydrosilane/ F^- reduction of β -keto amides provides threo aldols of high diastereomeric purity when aryl-substituted amides are employed.⁷ The scope of this reduction is summarized in Table II. High threo selectivity is observed only for reduction of 2-arylpropanoates, whereas the reduction of 2-alkanoylpropanoates proceeds with poor selectivity and gives erythro isomers as the major product.¹³ The

hydrosilane/F⁻ reduction is also applicable to the threo-selective reduction of α -oxy and α -amino ketones.⁸

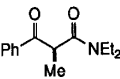
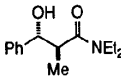
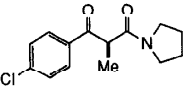
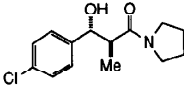
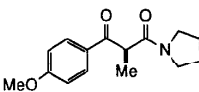
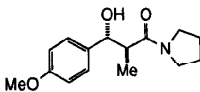
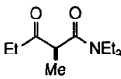
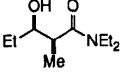
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TABLE I
ERYTHRO-SELECTIVE REDUCTION OF α -SUBSTITUTED β -KETO
ACID DERIVATIVES WITH $\text{PhMe}_2\text{SiH}/\text{H}^+$ REAGENT^a

Substrate ^b	Time, hr	Product ^c	% Yield ^d	Threo: Erythro ^e
	3		94	2 : 98
	20		89	1 : 99
	3		99	1 : 99
	3		87	1 : > 99

^aCarried out on a 0.5-1.0 mmol-scale at 0°C employing PhMe_2SiH (1.2 mol equiv) and CF_3COOH (1-2 mL/mmol). ^bRacemates were employed unless noted. ^cMajor isomers are shown. ^dPurified by silica gel chromatography. ^eThe ratio was determined by 90 or 400 MHz ^1H NMR analysis. ^fThe optically pure substrate was prepared according to a known method: Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

TABLE II
THREO-SELECTIVE REDUCTION OF β -KETO AMIDES
WITH $\text{PhMe}_2\text{SiH}/\text{F}^-$ REAGENT ^a

Substrate ^b	Time hr	Product ^c	% Yield ^d	Threo : Erythro ^e
	12		98	>99 : 1
	16		86	99 : 1
	16		92	99 : 1
	22		93	23 : 77

^aCarried out on a 0.5-1.0 mmol scale at 0°C employing PhMe_2SiH (1.2 mol equiv) and TASF (10 mol %). ^bRacemates were employed. ^cMajor isomers are shown. ^dPurified by silica gel chromatography. ^eThe ratio was determined by 90 or 400 MHz ^1H NMR analysis.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

erythro-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine: Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R*,R*)-(±) (11); (99114-36-0)

1-(2-Benzoylpropanoyl)piperidine: Piperidine, 1-(2-methyl-1,3-dioxo-3-phenylpropyl)-, (±) (11); (99114-34-8)

Propanoylpiperidine: Piperidine, 1-propionyl- (8); Piperidine, 1-(1-oxopropyl)- (9); (14045-28-4)

Propanoyl chloride: Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

Piperidine (8,9); (110-89-4)

Benzoyl chloride (8,9); (98-88-4)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

Dimethylphenylsilane: Silane, dimethylphenyl- (8,9); (766-77-8)β

Tris(diethylamino)sulfonium difluorotrimethylsilicate: Sulfur (1+). tris(N-ethyl-ethanaminato)-, difluorotrimethylsilicate (1-) (10); (59201-86-4)

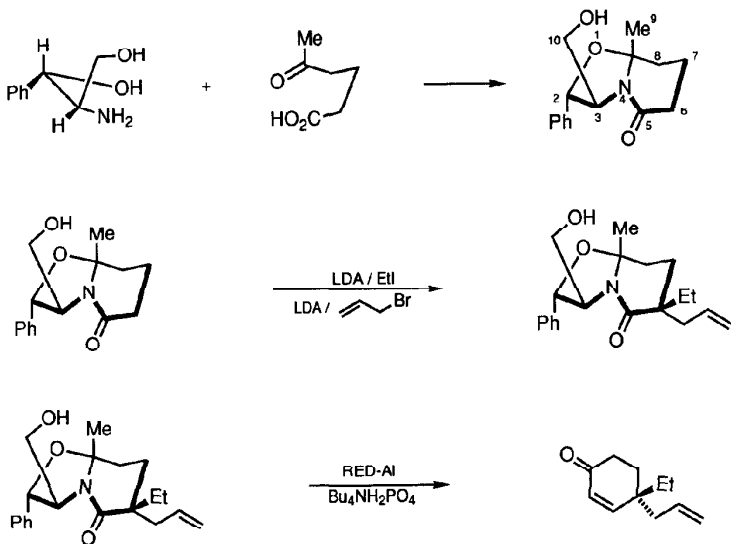
threo-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine, (R*,S*)-: Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R*,S*)- (±) (11); (99114-35-9)

1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone: 2(1H)-Pyrimidinone, tetrahydro-1,3-dimethyl- (8,9); (7226-23-5)

Diethylaminotrimethylsilane: Silanamine, N,N-diethyl-1,1,1-trimethyl- (8,9); (996-50-9)

Diethylaminosulfur trifluoride: Sulfur, (diethylaminato)trifluoro- (9); (38078-09-0)

**ASYMMETRIC SYNTHESIS OF 4,4-DIALKYL-CYCLOHEXENONES
FROM CHIRAL BICYCLIC LACTAMS:
(R)-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE**



Submitted by Albert I. Meyers and Daniel Berney.¹

Checked by P. B. Madan, A. Schwartz, and David L. Coffen.

1. Procedure

A. *Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine (Bicyclic lactam).* To a warm solution of (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol (32.4 g, 194 mmol) (Note 1) in toluene (800 mL), 5-oxo-

hexanoic acid (25 g, 912 mmol) (Note 2) is added with stirring. The stirred mixture is heated to reflux under argon with azeotropic removal of water for 18 hr. The reaction mixture is cooled, washed with 0.5 N hydrochloric acid (100 mL) and with saturated sodium bicarbonate solution (50 mL), dried over magnesium sulfate, and evaporated to dryness. The residue is crystallized from methylene chloride/hexane in the cold. The crystals are collected by filtration and washed with cold ether to give 35.9-37.2 g (71-74% yield) of the bicyclic lactam in two crops (Note 3).

B. Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,6S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine. In an oven-dried, 500-mL, round-bottomed flask, containing a magnetic stirring bar, is placed 14.4 g (55.2 mmol) of dry bicyclic lactam prepared in Part A. The flask is flushed with argon and filled with 150 mL of anhydrous tetrahydrofuran (Note 4) and then sealed with a rubber septum. The air in the flask is further replaced by argon (Note 5). After dissolution of the bicyclic lactam, the flask is cooled in dry ice/acetone and the solution is stirred while preparing lithium diisopropylamide (LDA).

To an oven-dried, 200-mL, conical flask (Note 6) with air replaced by argon, containing 50 mL of dry tetrahydrofuran (THF) and sealed with a rubber septum, 13.9 g (19.3 mL, 137.4 mmol) of diisopropylamine (Note 7) is added with a syringe. The flask is placed in an ice-water bath. After 15 min, 84 mL (134.4 mmol) of 1.6 M butyllithium in hexane (Note 8) is slowly added with a syringe and with gentle swirling of the flask. The solution is kept for 5 min at this temperature.

The lithium diisopropylamide solution prepared above is transferred dropwise, via a cannula, into the bicyclic lactam solution. The dry ice/acetone bath is replaced by an ice-water bath, where the reaction mixture is kept for 40 min to complete formation of the lithium enolate. The reaction mixture is cooled again (30 min) with a dry ice/acetone bath. Freshly distilled ethyl iodide (25.8 g, 13.4 mL, 165.4 mmol) (Note 9) is added slowly, via syringe, to the mixture and stirring is continued for 55 min in a

dry ice/acetone bath. The cooling bath is replaced by an ice-water bath, the mixture is stirred for exactly 40 min (Note 10), and is poured immediately into a separatory funnel containing 400 mL of 1.0 N hydrochloric acid. The resulting emulsion is extracted once with 400 mL of ether and the organic layer is washed with 200 mL of a 1:1 mixture of brine and a saturated solution of sodium bicarbonate. The ether extract is dried over magnesium sulfate and evaporated to dryness in a 500-mL round-bottomed flask. The residue is dissolved in 60 mL of dry toluene and evaporated again using a water bath (60°C for 45 min) to remove all traces of water and toluene. The product (17.2 g, > 100%) is used in the next step without further purification.

The 500-mL flask containing the crude dry product (17.2 g) is filled with argon and dry tetrahydrofuran (150 mL), a magnetic stirring bar is added, the flask is sealed with a rubber septum, and argon introduced once again. The flask is gently swirled until the viscous oil is totally dissolved and then the flask is immersed in a dry ice/acetone bath.

Another portion of LDA is prepared as described above except that this time 12.6 g of diisopropylamine (17.6 mL, 124.6 mmol) in THF (50 mL) and 78.0 mL (124.6 mmol) of 1.6 M butyllithium/hexane are used. The LDA solution is added, through a cannula, to the ethylated bicyclic lactam solution and the mixture is allowed to warm to 0°C; it is kept at this temperature for 3.0 hr (Note 11). The solution is cooled to -75° - -80°C in a dry ice/acetone bath. A solution of 9.4 g of freshly distilled allyl bromide (6.8 mL, 77.6 mmol) (Note 12) in dry THF (50 mL) is prepared in a 100-mL, oven-dried conical flask flushed with argon and sealed with a rubber septum. This solution is cooled in a dry ice/acetone bath and slowly added to the reaction mixture through a cannula (Note 13). After addition of the allyl bromide, the mixture is kept in a dry ice/acetone bath for 2.5 hr; then the bath is replaced by acetone at -50°C which is allowed to warm to -30°C within a period of 45 min (Note 14). The reaction is terminated by pouring it into 1 N hydrochloric acid (as above), extracting with ether,

washing with sodium bicarbonate-brine, drying over magnesium sulfate, and evaporating the solvents. The viscous or solid residue is dissolved in methylene chloride (10 mL), and petroleum ether (30-60°C) (140 mL) is added. The product is allowed to crystallize at room temperature for 1 hr, then at -15°C overnight, to give 13.5 g (74%, mp 90-92°C) of 9:1 mixture of diastereoisomers.

This mixture is recrystallized three times with the same mixture of solvents and the product is collected after 1 hr at 0°C to give 8.7 g (47.9%, mp 101-103°C) of a 25:1 mixture of diastereoisomers (values based on the 8a-methyl signal integration on NMR spectra) (Note 15).

C. *(R)*-4-Ethyl-4-allyl-2-cyclohexen-1-one. In an oven-dried, 500-mL, round-bottomed flask, containing dry toluene (300 mL) and a magnetic stirring bar, is placed the dialkylated lactam (7.6 g, 23.7 mmol). The solution is cooled in a dry ice/acetone bath and a 1 M solution of Red-Al in toluene (55 mL, 55.0 mmol) is slowly added (Note 16). The flask is flushed with argon and sealed with a rubber septum which is connected by a hypodermic needle to a rubber balloon filled with argon. The reaction mixture is allowed to warm to room temperature and stirred for 3 days. The septum is removed, the reaction mixture is cooled to 0°C, and methanol (10 mL) is cautiously added with stirring to destroy excess Red-Al. The solution is poured over 1 M aqueous potassium hydroxide (500 mL) in a 2-L separatory funnel and thoroughly shaken with ether (200 mL) until both layers become almost clear. The aqueous layer is extracted twice more with ether (2 x 100 mL) and, after the ethereal layers are combined, the ethereal solution is dried over magnesium sulfate and evaporated to dryness in a 500-mL flask.

The residue is dissolved in ethanol (250 mL), a 1 M aqueous solution of tetrabutylammonium dihydrogen phosphate (80 mL) (Note 17) is added, and the mixture is stirred under reflux for 24 hr. After the solution is cooled, it is partly evaporated on a rotary evaporator with a bath temperature not exceeding 40°C (Note

18) to remove most of the ethanol. Water is added (500 mL) and the solution is extracted twice with chloroform (200 mL). The chloroform extracts are washed with a 1:1 mixture of brine and 1 N hydrochloric acid and then with brine and saturated sodium bicarbonate solutions. Both aqueous phases are extracted twice with chloroform and the extracts are combined, dried over magnesium sulfate, and evaporated to dryness to give 5.8 g of crude 4,4-disubstituted cyclohexenone. The product is distilled rapidly in a Kugelrohr apparatus at 3.5 mm and 115°C to give 3.0 g (77%) of highly pure cyclohexenone (Note 19).

2. Notes

1. The amino diol was purchased from Aldrich Chemical Company, Inc. and was recrystallized before use from methanol/ethyl acetate (the material used had mp 111-113°C).

2. 5-Oxohexanoic acid was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

3. The bicyclic lactam thus prepared has the following physical properties: mp 98-99°C; $[\alpha]_D^{21} + 13.54^\circ$ (EtOH, *c* 1.55); IR (KBr) cm^{-1} : 3360, 2950, 1625, 1500, 1395; ^1H NMR (270 MHz, CDCl_3) δ : 3.75 (dd, C_{10}H , $J = 11.3, 8.5$), 3.90 (dd, C_{10}H , $J = 11.3, 1.9$) 4.07 (dt, C_3H , $J = 8.5, 1.9$), 4.79 (d, C_2H , $J = 8.6$), 4.89 (br s, 1 H, OH), 7.38 (s, 5 H, phenyl) and unresolved signals.

4. THF was distilled from a blue solution of benzophenone ketyl obtained by refluxing THF in the presence of a sodium dispersion in paraffin and benzophenone.

5. All reactions were done under argon atmosphere. The argon was introduced through hypodermic needles at a pressure below 50 mm across the rubber septum. An exhaust line was also provided to remove air or excess pressure.

6. A conical flask was used in order to allow efficient transfer of the LDA solution.

7. Commercial diisopropylamine was distilled over calcium hydride and stored over potassium hydroxide or 4 Å molecular sieves.

8. 1.6 M Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc.

9. Ethyl iodide was distilled over anhydrous potassium carbonate and stored in the refrigerator over copper turnings.

10. If the reaction mixture is kept for longer than 40 min in the ice water bath, undesirable amounts of the diethylated product are produced.

11. This is the minimum time to allow complete enolate formation.

12. Allyl bromide was distilled over anhydrous potassium carbonate and stored in the refrigerator over 4 Å molecular sieves.

13. The allyl bromide solution was allowed to cool efficiently by dripping it against the cold walls of the flask. It is important that allyl bromide reach the reaction mixture at the lowest possible temperature in order to obtain an optimal stereoselective alkylation. The cannula was protected against heat exchange with air by coating it with a fine rubber tubing.

14. Dry ice was removed leaving only acetone in the Dewar vessel. The temperature was then adjusted to -50°C by adding warm (room temperature) acetone; the temperature was allowed to rise slowly to -30°C by adding small portions of acetone.

15. The physical properties for the dialkylated bicyclic lactam are as follows:
[α]_D²¹ +38.89° (EtOH, *c* 1.77); IR (KBr) cm⁻¹: 3250, 2490, 1600, 1450, 1370, 1330, 1070, 890, 750; ¹H NMR (270 MHz, CDCl₃) δ : 0.91 (t, 3 H, C₁₂H, *J* = 7.3), 1.57 (s, 3 H, C₉H); 2.42 (ddd, 2 H, C₁₃H, *J* = 63.6, 13.4, 7.4), 3.65 (br, 1 H, OH), 3.75 (dd, C₁₀H, *J* = 11.3, 8.8), 3.90 (dd, C₁₀H, *J* = 11.2, 2.5), 4.13 (dt, C₃H, *J* = 8.8, 2.5), 4.78 (d, C₂H, *J* =

8.5), 5.11-5.16 (m, 2 H, C₁₅H), 5.73-5.88 (m, C₁₄H), 7.37 (s, 5 H, phenyl) and unresolved signals. Anal. Calcd for C₂₀H₂₇NO₃: C, 72.91; H, 8.26; N, 4.25. Found: C, 72.77; H, 8.25; N, 4.24.

16. 1 M Red-Al is prepared by diluting to 100 mL with toluene, 29.5 mL of commercially available 3.4 M Red-Al solution in toluene (Aldrich Chemical Company, Inc.; the checkers used Vitride brand supplied by Hexcel Corp.). Before use, this solution should be warmed to room temperature since it tends to separate into two layers at low temperatures. The first mL of Red-Al produces a vigorous evolution of gas; therefore, the flask should be kept open until the Red-Al addition is complete. Then the reaction vessel is sealed as described.

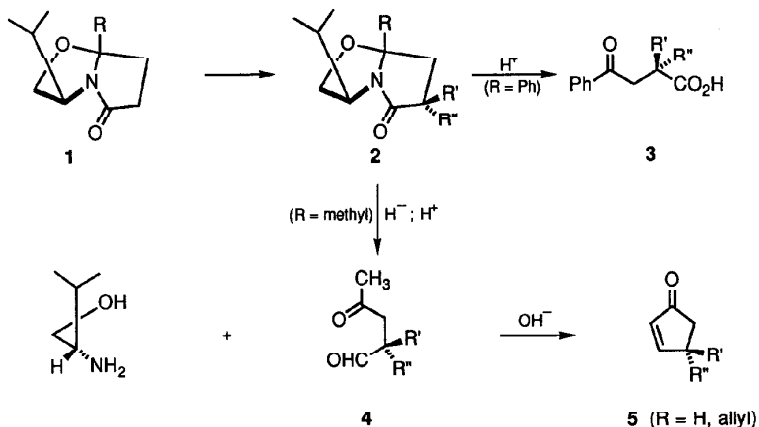
17. 1 M Tetrabutylammonium dihydrogen phosphate aqueous solution was purchased from Aldrich Chemical Company, Inc.

18. The product has a high vapor pressure and can easily be lost by evaporation. Thus, the yields will vary due to this property. The more caution exerted in the evaporation and distillation step, the higher will be the yield of product.

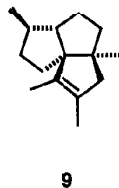
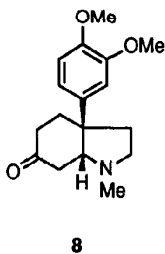
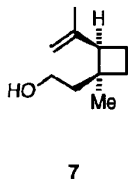
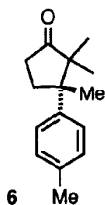
19. If the distillation is performed slowly, a substantial amount of the product may polymerize, resulting in lower yield. The physical data are as follows: $[\alpha]_D^{21} -23.12^\circ$ (EtOH, c. 1.67); IR (film) cm⁻¹: 2960, 1680, 1450, 1380, 1210; ¹H NMR (270 MHz, CDCl₃) δ : 0.95 (t, 3 H, C₈H, J = 7.6), 1.49-1.57 (m, 2 H, C₃H), 1.87 (t, 2 H, C₅H, J = 6.8), 2.23 (d, 2 H, C₉H, J = 6.6), 2.45 (t, 2 H, C₆H, J = 6.8), 5.07-5.14 (m, C₁₁H), 5.65-5.82 (m, C₁₀H), 5.94 (d, C₂H, J = 10.3), 6.71 (d, C₃H, J = 10.3). Anal. Calcd for C₁₁H₁₆O: C, 80.45; H, 9.82. Found: C, 79.67; H, 10.05. By GLC analysis, the product is 93-95% pure with 5-7% of diethylcyclohexenone detectable by GLC-MS.

3. Discussion

Chiral bicyclic lactams such as those described here are useful in reaching a variety of chiral quaternary carbon derivatives. Thus, **1** can be doubly alkylated to the



bicyclic lactam **2** in high diastereoselectivity. Acidic hydrolysis leads to α, α -substituted γ -keto acids **3**,² whereas reduction and hydrolysis furnish the chiral keto aldehydes **4**. Base-catalyzed aldolization affords chiral cyclopentenones **5**.³ In addition, several total syntheses of natural products have been accomplished, further demonstrating the synthetic usefulness of these bicyclic lactams **1**. Thus, (-)- α -cuparenone (**6**),⁴ (-)-grandisol (**7**),⁵ (+)-mesembrine (**8**),⁶ and (-)-silphiperfol-6-ene (**9**)⁷ have been prepared in high enantiomeric excess.



To reach chiral cyclohexenones, we have found that the bicyclic lactam **10**, derived from 5-oxohexanoic acid and the commercially available amino diol, gave excellent results. A number of examples were obtained (Table I).⁸

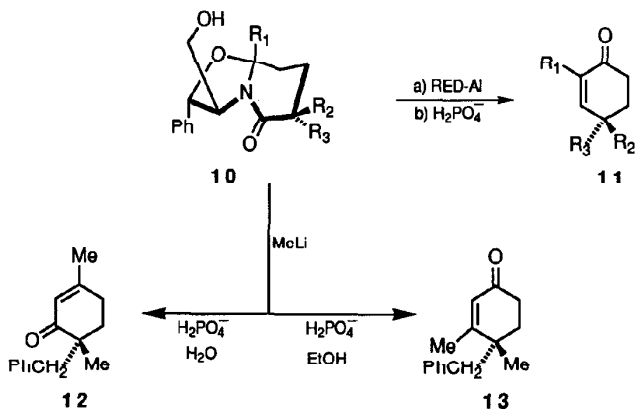


TABLE
CHIRAL 4,4-DIALKYLCYCLOHEXENONES (11)^a

10				11			
R ₁	R ₂	R ₃	R ₁	R ₂	R ₃	% Yield	[α] _D
Me	Me	PhCH ₂	H	Me	PhCH ₂	53	-65.6°
Me	PhCH ₂	Me	H	PhCH ₂	Me	68	+64.8°
Me	PhCH ₂	Allyl	H	PhCH ₂	Allyl	47	+48.9°
Et	Me	PhCH ₂	Me	Me	PhCH ₂	66	-39.7°
Me	Ph	Me	H	Ph	Me	47	+122.2°

^aYields refer to reduction and hydrolysis of **10** to **11**. All products are 99% optically pure (see ref. 8).

Furthermore, in place of reduction of **10** it was possible to add organolithium reagents such that the resulting alkyl carbinolamine, after hydrolysis, gave either **12** or **13** depending upon hydrolysis conditions.⁶ In summary, these bicyclic lactams have provided a route to a variety of chiral, nonracemic cyclohexenones and cyclopentenones containing quaternary stereocenters.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine: 5H-Oxazolo[3,2-a]pyridin-5-one, hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-, [2S-(2 α ,3 β ,8a β)]- (12); (116950-01-7)

(1S,2S)-(+)-2-Amino-1-phenyl-1,3-propanediol: 1,3-Propanediol, 2-amino-1-phenyl (9); (3306-06-7)

5-Oxohexanoic acid: Hexanoic acid, 5-oxo- (8,9); (3128-06-1)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Ethyl iodide: Ethane, iodo- (8,9); (75-03-6)

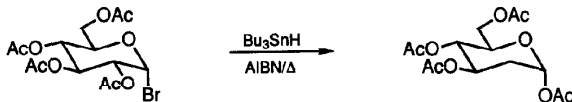
Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

Red-Al: Aluminate(1-), dihydrobis(2-methoxyethanolato)-, sodium (8); Aluminate(1-), dihydrobis(2-methoxyethanolato-O,O')-, sodium (9); (22722-98-1)

Tetrabutylammonium dicydrogen phosphate: Ammonium, tetrabutyl-, phosphate (1:1) (8); 1-Butanaminium, N,N,N-tributyl-, phosphate (1:1) (9); (5574-97-0)

1,3,4,6-TETRA-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSE

(α -D-arabino-Hexopyranose, 2-deoxy-, tetracetate)



Submitted by Bernd Giese and Kay S. Gröninger.¹

Checked by Matthew R. Sivik and Leo A. Paquette.

1. Procedure

A 1-L, round-bottomed flask equipped with a magnetic stirring bar, and a reflux condenser with a Claisen head on top fitted with a septum and dry nitrogen inlet, is charged with 20.6 g (50 mmol) of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (Note 1) and 400 mL of anhydrous toluene. The mixture is flushed with nitrogen and brought to reflux with a hot oil bath. A nitrogen atmosphere is maintained over the well-stirred reaction mixture during this and the ensuing steps. Meanwhile, a solution of 1.64 g (10 mmol) of azobisisobutyronitrile (AIBN) and 16.0 g (55 mmol) of tributylstannane in 90 mL of anhydrous toluene is prepared and filtered if necessary (Note 2). This solution is added to the refluxing, well-stirred reaction mixture during 6 hr by a syringe pump through a long needle which pierces the septum and ends at least 3 cm above the lower end of the cooling zone of the reflux condenser (Note 3). Ten minutes after all of the solution is added the reaction mixture is cooled and the solvent is removed with a rotary evaporator (bath 40°C); 100 mL of hexane and 100 mL of acetonitrile are added, and the resulting two-phase solution is stirred vigorously for 5 min and then transferred to a separatory funnel. The lower, acetonitrile layer is

separated and the hexane phase washed with 10 mL of acetonitrile (Note 4). This extraction of the combined acetonitrile solutions is repeated twice using 100 mL of hexane each time. The combined acetonitrile phases are then filtered and distilled (rotary evaporatory, bath 40°C). Coevaporation with 40 mL of hexane yields crude solid material which is dissolved in 120 mL of boiling tert-butyl methyl ether. Then 30 mL of hexane is added and the mixture left for 4 hr at room temperature. To complete crystallization of the product another 20 mL of hexane is added and the mixture is kept for 12 hr at 5°C. The long colorless needles are filtered and washed once with 30 mL of hexane/tert-butyl methyl ether (2:1) and two times with 30 mL of pentane to yield 13.2-13.4 g (79-81%) of 1,3,4,6-tetra-O-acetyl-2-deoxy- α -D-glucopyranose, mp 109-110°C [α]_D²⁰ +113° (C₂H₅OH, c 1.2).

2. Notes

1. This material was obtained from the Sigma Chemical Company and was recrystallized from diethyl ether/pentane before use. It can also be prepared by the procedure of Redemann, C. E.; Niemann, C. *Org. Synth., Coll. Vol. III* 1955, 11.

2. Azobisisobutyronitrile (AIBN) and tributylstannane were obtained from the Aldrich Chemical Company, Inc. The amount of AIBN can be reduced to 0.82 g (5 mmol) without affecting yields. A small excess (1.1 to 1.2 equiv) of tributylstannane must be used to ensure total consumption of starting material.

3. This method ensures that AIBN is not thermolized in the needle and that tributylstannane is diluted by the refluxing solvent before reaching the reaction mixture. It is also possible to add the tributylstannane solution by a dropping funnel (1 drop every 2 seconds) which replaces septum and syringe pump. This method gives

only slightly lower yields (75%) if the stannane solution runs down slowly on the glass surface of the condenser and does not enter the reaction mixture undiluted.

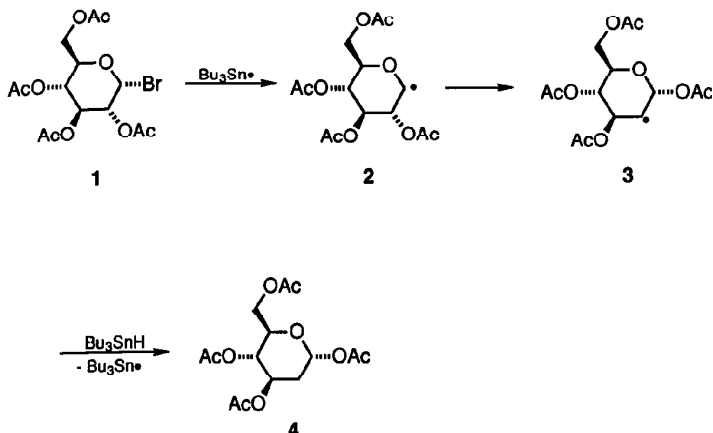
4. By this procedure most of the tributylbromostannane, and other stannyl compounds are removed. It is important to wait for complete separation of the phases.

5. The product is analytically pure, Anal., Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.71; H, 6.25. 1H NMR (300 MHz, $CDCl_3$) δ : 1.97 (ddd, 1 H, H-2a; $J_{1,2a} = 3.7$, $J_{2a,2c} = 13.6$, $J_{2a,3} = 11.6$); 2.04, 2.05, 2.09, 2.14 (4 s, 12 H, acetyl); 2.28 (ddd, 1 H, H-2e, $J_{1,2e} = 1.4$, $J_{2e,3} = 5.3$); 4.00-4.11 (m, 2 H, H-5, H-6); 4.36 (m, 1 H, H-6"); 5.08 (t, 1 H, H-4, $J_{3,4} = J_{4,5} = 9.7$); 5.32 (ddd, 1 H, H-3); 6.26 (br d, 1 H, H-1).

6. Concentration of the mother liquors gives another 0.4-0.6 g of impure product which can be recrystallized from tert-butyl methyl ether/hexane to give another 0.3-0.5 g (2-3%) of analytically pure product.

3. Discussion

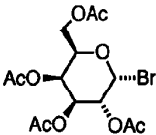
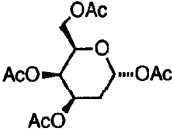
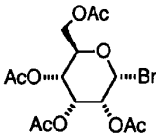
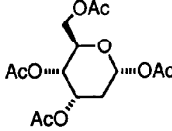
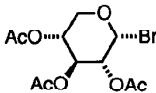
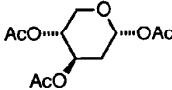
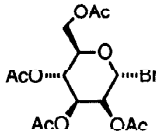
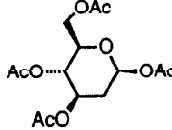
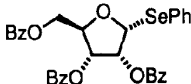
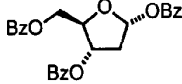
The main reaction step of this synthesis of 2-deoxy sugars is a radical rearrangement ($2 \rightarrow 3$).² Bromine abstraction from the glucosyl bromide **1** by tributyltin radicals yields glucosyl radical **2** that undergoes acetoxy migration and gives the rearranged radical **3**. This rearrangement is a stereoselective one-step reaction that occurs with rate coefficients of about 10^3 at 75°C in benzene.³ The driving force of the rearrangement $2 \rightarrow 3$ is the formation of the acetal structure at C-1 of **3**.⁴ Hydrogen abstraction from tributyltin hydride yields 2-deoxy sugar **4** and the tributyltin radical that starts another chain.



This rearrangement offers a general synthesis of α - and β -2-deoxy sugars with pyranoid and furanoid ring systems (Table).⁵

1. Institut für Organische Chemie, TH Darmstadt, Petersenstrasse 22, D-6100 Darmstadt, Germany.
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TABLE
Synthesis of 2-Deoxy Sugars
via Reductive Rearrangement of Glycosyl Derivatives⁵

Glycosyl Bromide	2-Deoxy Sugar	Yield(%)
		71
		70
		81
		66
		75

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,3,4,6-Tetra-O-acetyl-2-deoxy- α -D-glucopyranose: D-arabino-Hexopyranose, 2-deoxy-, tetraacetate, α - (8); α -D-arabino-Hexopyranose, 2-deoxy-, tetraacetate (9); (16750-06-4)

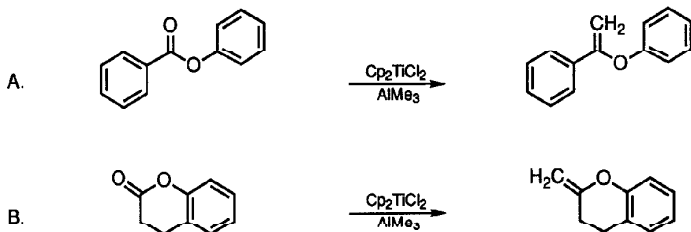
2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide: Glucopyranosyl bromide, tetraacetate, α -D- (8); α -D-glucopyranosyl bromide, 2,3,4,6-tetraacetate (9); (572-09-8)

Azobisisobutyronitrile: Propionitrile, 2,2'-azobis[2-methyl- (8); Propanenitrile, 2,2'-azobis[2-methyl- (9); (78-67-1)

Tributylstannane: Stannane, tributyl- (8,9); (688-73-3)

THE SYNTHESIS OF ENOL ETHERS BY METHYLENATION OF ESTER
1-PHENOXY-1-PHENYLETHENE AND 3,4-DIHYDRO-2-METHYLENE-
2H-1-BENZOPYRAN

(Ether, phenyl 1-phenylvinyl) and 2H-1-Benzopyran, 3,4-dihydro-
2-methylene-)



Submitted by Stanley H. Pine,^{1a} Gia Kim,^{1b} and Virgil Lee.

Checked by Roger B. Ruggeri and Clayton H. Heathcock.

1. Procedure

A. 1-Phenoxy-1-phenylethene. To a 250-mL round-bottomed flask (Note 1) equipped with a magnetic stirring bar is added 5.0 g (20.0 mmol) of titanocene dichloride [bis(cyclopentadienyl)titanium dichloride] (Note 2). The flask is fitted with a rubber septum through which a large-gauge needle is passed to flush the system with dry nitrogen. After the vessel has been thoroughly purged, the nitrogen line flowing to the needle is opened to a mineral oil bubbler and 20 mL of a trimethylaluminum solution (2.0 M in toluene, 40 mmol) is added by a nitrogen-purged syringe (Note 3). Methane gas evolved by the reaction is allowed to vent as the resulting red solution is stirred at room temperature for 3 days. The Tebbe reagent² thus formed is used in situ

by cooling the mixture in an ice-water bath (Note 4), then adding 4.0 g (20 mmol) of phenyl benzoate (Note 5) dissolved in 20 mL of dry tetrahydrofuran (Note 6) by syringe or cannula to the cooled stirring solution over 5-10 min. After the addition, the reaction mixture is allowed to warm to room temperature and is stirred for about 30 min. The septum is removed and 50 mL of anhydrous diethyl ether is added. To the stirring reaction mixture is gradually added 50 drops of an aqueous solution of 1 M sodium hydroxide over 10 to 20 min (Note 7). Stirring is continued until gas evolution essentially ceases; then to the resulting orange slurry are added a few grams of anhydrous sodium sulfate to remove excess water. The mixture is filtered through a Celite pad on a large coarse frit using suction and liberal amounts of diethyl ether to transfer the product and rinse the filter pad. Concentration of the filtrate with a rotary evaporator (Note 8) to 5-8 mL provides crude product, which is purified by column chromatography on basic alumina (150 g) eluting with 10% diethyl ether in pentane (Note 9). Fractions which contain product (Note 10) are combined and evaporated to give 2.69-2.79 g (68-70%) of the desired enol ether (Note 11) as a pale yellow oil.

B. 3,4-Dihydro-2-methylene-2H-1-benzopyran. Formation of the exo-methylene enol ether with dihydrocoumarin is carried out as in the foregoing procedure except that the reaction solution is cooled with a dry ice-acetone bath before addition of the lactone. From 3.0 g (20 mmol) of dihydrocoumarin (Note 5) is obtained 1.85-1.97 g (63-67%) of the product (Note 12) as a pale yellow oil, after column chromatography on basic alumina (150 g) eluting with 5% diethyl ether in pentane.

2. Notes

1. The checkers found that the acid liability of the enol ether products requires rigorous treatment of all glassware used for the reaction in order to avoid migration of the double bond in susceptible cases (e.g., dihydrocoumarin in Preparation B). Satisfactory results were obtained by treating the glassware sequentially with ethanolic 0.5 M solutions of hydrogen chloride and potassium hydroxide for approximately 1 hr, thoroughly rinsing with distilled water after each treatment and finally oven drying. This protocol is also effective for removing stubborn deposits on the glassware used for the reaction.

2. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc. and used without further purification. This compound is normally obtained as bright red crystals. If its purity is in question Soxhlet extraction using dichloromethane is usually effective; titanocene dichloride is slightly soluble in dichloromethane and slowly dissolves from insoluble materials present.

3. Trimethylaluminum was purchased from Aldrich Chemical Company Inc. and obtained as a 2.0 M solution in toluene sealed under nitrogen in a Sure/Seal bottle. Trimethylaluminum is pyrophoric and reacts violently with water and air; the syringe and needle used should be rinsed with toluene or hexanes immediately after addition. Note that the rinse, though dilute, contains pyrophoric material and should be handled accordingly.

4. Reaction with the ester is relatively exothermic. Sensitivity of the substrate-product to heating varies and should be considered for each particular compound. Phenyl benzoate can be methylenated at room temperature with no significant decrease in product yield. By contrast, dihydrocoumarin (Preparation B) gives no product under these conditions and must be methylenated at -78°C to obtain a good yield. For most substrates it is satisfactory to carry out reactions at 0°C .

5. Substrate esters were purchased from Aldrich Chemical Company, Inc. and used without further purification.

6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.

7. Evolution of methane can be quite vigorous so that the reaction vessel must be large enough to prevent bubbling over. If the aqueous solution is delivered slowly in 10-drop increments over the addition period a controlled quench of the reaction mixture is possible. Cooling slows gas evolution, but also greatly prolongs the hydrolysis step.

8. Methylene enol ethers are usually lower boiling than their ester precursors. Low molecular weight products can be easily lost in evaporation; therefore the toluene must be removed with care.

9. The checkers used Fisher Scientific basic alumina, Brockman activity I, 80-200 mesh. Neutral alumina and silica gel have also been used. Basic alumina minimizes the potential hazards of hydrolysis or proton-catalyzed isomerization of the carbon-carbon double bond in susceptible enol ethers. Gaseous trimethylamine has also been added to the eluent to minimize these problems during purification.

10. The checkers eluted the columns with a slight positive air pressure on the solvent reservoir to prevent formation of gas bubbles and cracks in the chromatographic medium. Fractions were collected in 25-mL test tubes (Note 1), analyzed by TLC on silica gel, eluting with the column solvent, and visualized with a phosphomolybdic acid solution. The checkers observed a nonvolatile hydrocarbon material (not substrate related) which was eluted in the fractions just prior to the products, which are quite nonpolar themselves and are eluted in the early fractions, ahead of any unreacted ester. Colored, metal-containing components usually remain near the top of the column, although some colored material may accompany the

product if much toluene remains in the sample or if the sample is applied to the column in a more polar solvent.

11. The spectral properties for 1-phenoxy-1-phenylethene are as follows: IR (film) cm^{-1} : 1600, 1495, 1290, 1230; ^1H NMR (250 MHz, CDCl_3) δ : 4.45 (d, 1 H, $J = 2.3$), 5.05 (d, 1 H, $J = 2.3$), 7.06-7.11 (m, 3 H), 7.29-7.38 (m, 5 H), 7.66-7.70 (m, 2 H).

12. While the submitters observed no complications, the checkers were unable, even after many trials, to obtain the dihydrocoumarin adduct completely free of what appears to be the product of double bond migration to give the endocyclic enol ether. Initial results were quite erratic. However, use of the glassware treatment described in Note 1, suggested by Professor Pine, has consistently provided the desired compound contaminated with only a few percent of the unwanted isomer. Spectral properties for the 3,4-dihydro-2-methylene-2H-1-benzopyran are as follows: IR (film) cm^{-1} : 1665, 1595, 1500, 1470, 1250, 990, 770; ^1H NMR (250 MHz, CDCl_3) δ : 2.57 (t, 2 H, $J = 6.5$), 2.80 (t, 2 H, $J = 6.5$), 4.14 (s, 1 H), 4.55 (s, 1 H), 6.85-6.92 (m, 2 H), 7.03-7.07 (m, 1 H), 7.11-7.18 (m, 1 H); impurity (partial) δ : 1.88 (bs, 3 H), 3.39 (bs, 2 H), 4.70 (bs, 1 H).

3. Discussion

The formation of carbon-carbon bonds through the condensation of carbonyl compounds with phosphoranes (the Wittig reaction) is a very useful method in organic synthesis.³ Allowing the convergence of a wide variety of substrates enables this reaction to provide considerable flexibility in product design. Yet, with limited exceptions,⁴ this process has not been effective for the transfer of methylene or alkylidenes to the carbonyl group of esters or other carboxylic acid derivatives. However, reaction of the titanium-aluminum complex (the Tebbe reagent)² described here does transfer a methylene to the carbonyl group of esters, effecting the conversion of an ester to an enol ether.⁵

The Tebbe reagent functions as a nucleophilic carbenoid in its reactions with carbonyl groups. The carbenoid is activated in the presence of a Lewis base which presumably complexes with the aluminum atom. Tetrahydrofuran is the Lewis base in the reactions described above. If the reaction is performed in the absence of added tetrahydrofuran, the carbonyl oxygen atom can function as a weak Lewis base, although the methylenation process is considerably slower.

Vinyl ethers have also been prepared by addition of alkoxides to acetylene,^{6,7,8} elimination from halo ethers and related precursors,^{6,8} and vinyl exchange reactions.⁸ Reaction of an electrophilic tungsten carbenoid with methylene phosphorane or diazomethane also produces vinyl ethers.⁹ Enol ethers have resulted from the reaction of some tantalum and niobium carbenoids with esters,¹⁰ and the reaction of phosphoranes with electrophilic esters.⁴

Methylenation using the titanium-aluminum complex converts a variety of esters to enol ethers in good yields.⁵ Lactones are converted to synthetically useful exomethylene enol ethers. Carbon-carbon double bonds do not interfere with the methylenation reaction, although functional groups containing acidic hydrogen atoms do consume the reagent and should be protected. The carbonyl group of aldehydes and ketones reacts in preference to the ester carbonyl group in the methylenation process,^{5b} but those groups can also be selectively protected.

Because of the expense of obtaining the Tebbe reagent in its pure form,¹¹ an in situ method for its preparation and use was developed.¹² The presence of the excess Lewis acidic by-product, dimethylaluminum chloride, in the in situ preparation may cause reactivity at other sites in the substrate or lower yields of desired products (e.g., 70% vs. 94% for Preparation A, and 65% vs. 85% for Preparation B).^{5b} However the overall simplicity of the method can be advantageous with readily obtained substrates.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Phenoxy-1-phenylethene: Ether, phenyl 1-phenylvinyl (8,9); (19928-57-5)

3,4-Dihydro-2-methylene-2H-1-benzopyran: 2H-1-Benzopyran, 3,4-dihydro-2-methylene- (10); (74104-13-5)

Titanocene dichloride: Titanium, dichloro- π -cyclopentadienyl- (8); Titanium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1271-19-8)

Trimethylaluminum: Aluminum, trimethyl- (9); (75-24-1)

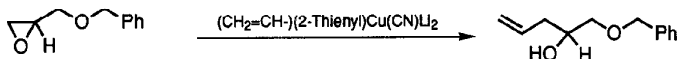
Phenyl benzoate: Benzoic acid, phenyl ester (8,9); (93-99-2)

Dihydrocoumarin: 2H-1-Benzopyran-2-one, 3,4-dihydro- (9); (119-84-6)

MIXED HIGHER ORDER CYANOCUPRATE-INDUCED EPOXIDE

OPENINGS: 1-BENZYLOXY-4-PENTEN-2-OL

(4-Penten-2-ol, 1-(phenylmethoxy)-)



Submitted by Bruce H. Lipshutz,¹ Robert Moretti, and Robert Crow.

Checked by Gary L. Bolton, Steven G. Toske, and James D. White.

1. Procedure

A 100-mL, two-necked, round-bottomed flask (Note 1), equipped with a stirring bar and a rubber septum is evacuated and flame-dried under vacuum, then flushed with dry argon. This process is repeated 3 times. Anhydrous tetrahydrofuran (36 mL, Note 2) and distilled thiophene (3.05 g, 2.91 mL, 36.3 mmol, Note 3) are injected via syringe and the resulting solution is cooled to -78°C . Butyllithium in hexanes (12.8 mL, 2.83 M, 36.3 mmol, Note 4) is added dropwise via syringe. The resulting light yellow solution is warmed to -20°C using a solid dry ice/carbon tetrachloride bath and stirred for 30 min.

A 500-mL, two-necked, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with copper(I) cyanide (2.95 g, 33.0 mmol, Note 5). The flask is evacuated and gently flame-dried under vacuum (Note 6), then flushed with dry argon. The process is repeated 3 times. Anhydrous tetrahydrofuran (33 mL) is injected and the resulting slurry is cooled to -78°C . At this time, the previously prepared solution of 2-lithiothiophene in tetrahydrofuran (at -20°C) is added via cannula to the stirring slurry. At the end of the addition, the acetone-dry ice bath is

exchanged for an ice bath. After 5 min (Note 7), the flask is again placed in a dry ice-acetone bath. Vinyl lithium in tetrahydrofuran (16.7 mL, 1.98 M, 33.0 mmol, Note 8) is added dropwise after 15 min. Then the -78°C bath is exchanged for an ice bath. After 5 min, the reaction mixture is recooled to -78°C and a cooled (-20°C) solution of benzyl 2,3-epoxypropyl ether (4.93 g, 30.0 mmol, Note 9) in anhydrous tetrahydrofuran (30 mL) is added to the cuprate solution via cannula over a period of 10 min. The reaction mixture is warmed to 0°C (Note 10). After 3 hr at 0°C , it is warmed to ambient temperature and stirred 1 more hr. It is then cooled to -78°C and poured on to a solution of saturated aqueous ammonium chloride (135 mL) and concentrated aqueous ammonium hydroxide (15 mL). The mixture is stirred for an additional 15 min while the temperature of the system is allowed to rise. The mixture is filtered through Celite. The flask and the filter cake are rinsed with tetrahydrofuran (2 x 20 mL). The tetrahydrofuran is evaporated using a rotary evaporator and the resulting aqueous layer is extracted with ethyl acetate (2 x 150 mL). Each organic layer is washed with water (75 mL) and brine (75 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residue is purified by column chromatography on silica gel (Note 11), using a 6:1 mixture of petroleum ether and ethyl acetate as eluent (Note 12), to afford an oil (5.7 g, 29.6 mmol, 99%) which is distilled through a short-path distillation apparatus to give 4.20 g of an oil (26.1 mmol, 73%) (Note 13) as a colorless liquid, bp 85°C at 0.1 mm; IR (neat) cm^{-1} : 3400, 3070, 3030, 1640, 1100, 740, 700; ^1H NMR (CDCl_3) δ : 2.26 (t, 2 H, $J = 6.9$), 2.41 (d, 1 H, $J = 3.3$), 3.4-3.6 (m, 2 H), 3.90 (m, 1 H), 4.55 (s, 2 H), 5.1 (m, 2 H), 5.75-5.90 (m, 1 H), 7.33 (s, 5 H); mass spectrum, m/e (relative intensity): 192 (M^+ , 1.06), 92 (24.89), 91 (100); high resolution mass spectrum, Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$: 192.1150. Found: 192.1161.

2. Notes

1. All glassware, needles and syringes are stored in an oven at 120°C overnight and assembled while hot.

2. Tetrahydrofuran is distilled from sodium-benzophenone before use.

3. Thiophene is purchased from the Aldrich Chemical Company, Inc. and distilled from calcium hydride before use.

4. Butyllithium in hexanes (2.5 M) is purchased from the Aldrich Chemical Company, Inc. and titrated with 2-pentanol in ether, using 1,10-phenanthroline as indicator before use.² Use of lower concentrations of butyllithium for the metalation of thiophene under these conditions results in incomplete lithiation.

5. Copper(I) cyanide is purchased from the Aldrich Chemical Company, Inc. and is dried in an Abderhalden apparatus at 56°C for ca. 2 days before use. *Caution: Copper(I) cyanide is very toxic.*

6. *Caution should be exercised during this operation. Overheating can result in partial decomposition of the copper(I) cyanide.*

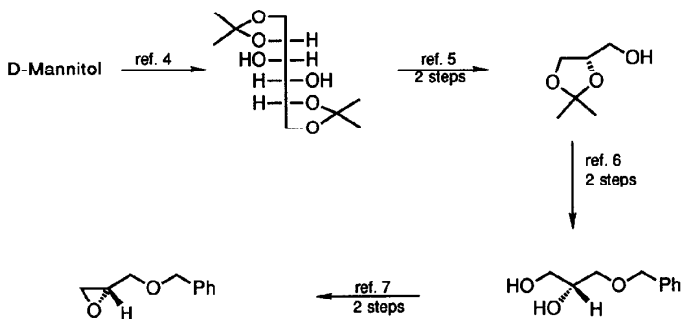
7. At this point, all of the copper(I) cyanide has been consumed and the reaction appears as a brown solution.

8. Vinylolithium in tetrahydrofuran is purchased from Organometallics, Inc., and titrated² before use (see Note 4).

9. The starting material was prepared by the benzylation of glycidol, with benzyl bromide in tetrahydrofuran according to the following procedure: A 500-mL, two-necked, round-bottomed flask equipped with a stirring bar and a rubber septum is evacuated and flame-dried under vacuum, then flushed with dry argon. This process is repeated three times. A solution of distilled glycidol (4.0 g, 3.58 mL, 54 mmol, obtained from Aldrich Chemical Company, Inc. and distilled before use) in anhydrous tetrahydrofuran (139 mL) is injected via syringe and the resulting clear solution is

cooled to 0°C. Sodium hydride (2.24 g of a 60% dispersion in mineral oil, 56 mmol, obtained from Aldrich Chemical Company, Inc.) is added portionwise and the resulting gray mixture is stirred at 0°C for 30 min. Solid tetrabutylammonium iodide (0.21 g, 0.56 mmol, obtained from Aldrich Chemical Company, Inc.) is then introduced all at once. Distilled benzyl bromide (9.54 g, 6.63 mL, 55.8 mmol) is added (neat) dropwise via syringe. [Benzyl bromide was purchased from the Aldrich Chemical Company, Inc. and dried over MgSO₄, filtered, and distilled before use (*Caution: Benzyl bromide is light sensitive and is a potent lachrymator*).] The solution is stirred at 0°C for 5 min, then warmed to ambient temperature and stirred for 1 hr. The mixture is quenched with aqueous ammonium chloride and extracted with ethyl acetate (2 x 200 mL). Each organic phase is washed with water (100 mL) and brine (2 x 100 mL). The combined organic layers are dried over sodium sulfate and concentrated using a rotary evaporator. The remaining yellow residue is purified by flash chromatography,³ using a 5:1 mixture of petroleum ether and ethyl acetate as eluent, to afford chromatographically pure (±)-benzyl 2,3-epoxypropyl ether (7.34 g, 44.7 mmol, 83%) which can be distilled through a short-path distillation apparatus to give 6.52 g of the epoxide (39.7 mmol, 74%) as a colorless liquid, bp 105°C at 0.4 mm.

Optically active (S)-benzyl 2,3-epoxypropyl ether can be obtained in quantity in seven steps from D-mannitol according to literature procedures.⁴⁻⁷



10. At this point, the color of the solution turns from brown to light green, and darkens with time.

11. The technique of Still³ (flash chromatography) is used, with silica gel purchased from ICN Biomedicals (ICN Silica 21-63).

12. For TLC analyses, Merck silica gel F-254 TLC plates were used, with 1:1 petroleum ether-ether as eluent. Visualization was effected by spraying with a 5% phosphomolybdic acid in ethanol solution followed by heating at ca. 250°C on a hot plate. (R)-1-Benzyloxy-4-penten-2-ol has an R_f of ca. 0.35 in this solvent system.

13. The checkers found that there was consistently 10-12% of 1-benzyloxyheptan-2-ol in the reaction mixture resulting from coupling of "residual" butyllithium (which forms $n\text{-Bu(Th)Cu(CN)Li}_2$) with the epoxide.

3. Discussion

This procedure is an illustration of the use of mixed, higher order (H.O.) cyanocuprates containing a non-transferable or "dummy" ligand for epoxide opening.⁸ H.O. cuprates of general stoichiometry $R_T(2\text{-thienyl)Cu(CN)Li}_2$ can also be used to

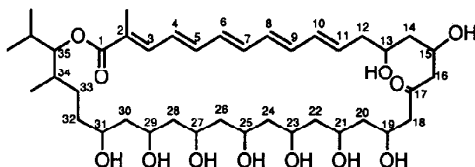
effect substitution reactions with halides, as well as conjugate additions to unhindered α,β -unsaturated ketones (see Table).⁸

The lower order (L.O.) cyanocuprate (2-Th)Cu(CN)Li has an excellent shelf life, thereby providing a highly stable precursor to higher order cuprates.⁹ Tetrahydrofuran solutions of this L.O. cuprate are available commercially (from Aldrich Chemical Company, Inc.), thus allowing further simplification of this procedure.

The often greater reactivity of H.O. cuprates¹⁰ as compared to their L.O. counterparts is exemplified by this method. When (vinyl)₂CuLi (from 2 vinyl lithium + 1 CuI, a Gilman type reagent)¹¹ was used for the same transformation, a yield of 73% was observed, along with recovered starting material.¹² The L.O. cyanocuprate (vinyl)Cu(CN)Li gave only 11% of the desired product.⁸ Significantly, in the procedure described only 1.1 equivalents of H.O. cuprate are necessary for complete consumption of the epoxide.

The (R)-1-benzyloxy-4-penten-2-ol produced using enantiomerically-enriched starting material in this reaction is a useful precursor in the synthesis of the polyol section of the polyene macrolide antibiotic roflamycoin (Scheme 1). This molecule

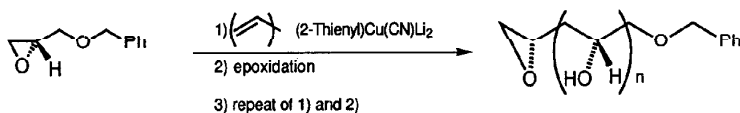
Scheme 1



Roflamycin

has an array of 1,3-secondary hydroxyl groups, assumed to bear an all-syn relationship to each other, for which a synthetic strategy has been devised.¹²⁻¹⁴ Thus, a reiterative 2-step protocol involving epoxide opening with a H.O. vinylocyanocuprate, followed by stereoselective homoallylic alcohol epoxidation, reforms the functionality (i.e., an epoxide) from which it was originally derived (Scheme 2).

Scheme 2



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Benzyloxy-4-penten-2-ol: 4-Penten-2-ol, 1-(phenylmethoxy)- (9); (58931-16-11)

Thiophene (8,9); (110-02-1)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Copper(I) cyanide: Copper cyanide (8,9); (544-92-3)

Vinylolithium: Lithium, vinyl- (8); Lithium, ethenyl- (9); (917-57-7)

Benzyl 2,3-epoxypropyl ether: Propane, 1-(benzyloxy)-2,3-epoxy- (8); Oxirane, [(phenylmethoxy)methyl]- (9); (2930-05-4)

Glycidol: 1-Propanol, 2,3-epoxy- (8); Oxiranemethanol (9); (556-52-5)

Benzyl bromide: Toluene, α -bromo- (8); Benzene, (bromomethyl)- (9); (100-39-0)


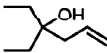
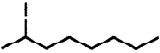
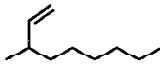

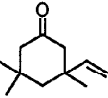

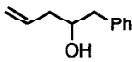
Tetrabutylammonium iodide (8); 1-Butanaminium, N,N,N-tributyl-, iodide (9); (311-28-4)

(S)-Benzyl 2,3-epoxypropyl ether: Propane, 1-(benzyloxy)-2,3-epoxy-, (S)- (8,9); (14618-80-5)

D-Mannitol (8,9); (69-65-8)

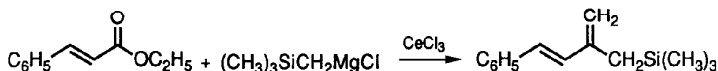
Table

Reactions of Various Substrates with (Vinyl)(2-thienyl)Cu(CN)Li₂.

Substrate	Equiv. of cuprate	Conditions	Product	Yield(%)
	1.20	THF/Et ₂ O room temp. 4 hr		71 ^a
	1.50	THF, 31° 18 hr		67 ^b
	1.10	THF/Et ₂ O 1.1 eq. BF ₃ -78°, 1 hr		98 ^b
	1.25	THF/Et ₂ O 0°, 1 hr		90 ^a

^aIsolated yield of chromatographically pure material. ^bBy quantitative GC analysis.

THE CONVERSION OF ESTERS TO ALLYLSILANES:
TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE
(Silane, trimethyl (2-methylene-4-phenyl-3-butenyl)-)



Submitted by William H. Bunnelle and B. A. Narayanan.¹

Checked by Jürgen Fischer and Ekkehard Winterfeldt.

1. Procedure

A 1-L, three-necked, round-bottomed flask with mechanical stirrer and vacuum outlet (Note 1) is charged with powdered cerium(III) chloride ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, 52.92 g, 0.142 mol) (Note 2). The flask is immersed to the necks in an oil bath and evacuated to 0.2 mm. The solid is agitated by stirring as the flask is heated to 150°C for 2 hr. After the flask is cooled to room temperature, it is vented to the atmosphere, and quickly purged with a stream of dry nitrogen for 2 min. At this stage, the flask is fitted with a low-temperature thermometer and a graduated 250-mL addition funnel containing 300 mL of dry tetrahydrofuran (THF) (Note 3), and capped with a rubber septum. Connection to a dry nitrogen line with a pressure relief bubbler is made via a needle through the septum. Tetrahydrofuran is run into the flask with good stirring, so that an even suspension results (Note 4). The white suspension is stirred at room temperature for 2 hr. Meanwhile, the addition funnel is charged with trimethylsilylmethylmagnesium chloride ($\text{Me}_3\text{SiCH}_2\text{MgCl}$, 1 M solution in ethyl ether, 142 mL, 0.142 mol) (Notes 5 and 6), transferred via stainless steel cannula. The contents of the flask are cooled to -65°C with a dry ice-2-propanol bath, and the

Grignard solution is added dropwise over a period of 40-50 min, so that the temperature of the reaction mixture remains below -60°C . The addition funnel is removed from the setup, with the septum/nitrogen inlet connected directly to the flask. After the cold mixture is stirred for 15 min more, ethyl cinnamate (10.32 g, 0.0586 mol) (Note 7) is added via syringe over a 2-3 min period. Stirring is continued as the flask is allowed to warm slowly to room temperature (Note 8). The off-white to beige reaction mixture is cooled to $<5^{\circ}\text{C}$ (ice-water bath) and quenched by the portion-wise addition of chilled 1 M hydrochloric acid (200 mL), so that the internal temperature remains below 20°C (Note 9). The layers are separated, and the aqueous phase is extracted twice with ethyl ether (100 mL each). The combined organic layers are washed with saturated sodium bicarbonate solution (Note 10), dried over sodium sulfate, and the solvents are removed at a rotary evaporator ($25^{\circ}\text{C}/60$ mm). The residual oil is transferred to a 100-mL, round-bottomed flask and distilled bulb-to-bulb (Note 11). The product (9.69-9.85 g, 76.5-78%) (Note 12) is collected at an air bath temperature of $110\text{-}112^{\circ}\text{C}$, 0.20 mm.

2. Notes

1. The vacuum outlet should be packed with glass wool, to prevent loss of significant quantities of cerium salt during the drying process. During some runs, cerium salts worked into the stirrer shaft bearing, causing it to bind. This problem could be avoided by placing a straight adapter tube between the bearing and the flask, to distance the bearing from the reaction mixture. The checkers found that sublimation of the cerium salt occurred in all their runs, but did not appear to affect the yield.

2. Cerium(III) chloride heptahydrate was purchased from Aldrich Chemical Company, Inc., and ground with a mortar and pestle just before use.

3. Tetrahydrofuran was freshly distilled under nitrogen from sodium and benzophenone. The (nominal) 250-mL funnel holds the entire volume of solvent.

4. On one occasion, when the solvent was added without stirring, the solid formed a hard cake on the bottom of the flask, and resisted attempts to bring it into suspension. The full 2 hr 'ageing' period is necessary for best results.

5. This clear, pale yellow solution was purchased from the Aldrich Chemical Company, Inc. The Grignard solution may be prepared from trimethylsilylmethyl chloride.² Take care to prevent air oxidation in opened bottles of the Grignard reagent -- these solutions deteriorate rapidly, and older samples are unsuitable for the present procedure.

6. The prescribed quantity of Grignard reagent (and cerium salt) is 25% more than stoichiometric. This excess is required to ensure complete consumption of the ester.

7. Ethyl cinnamate was purchased from Eastman Kodak Company, and was distilled at 110-111°C/0.75 mm before use.

8. Warming takes approximately 3 hr. The reaction is complete by this time and can be worked up. Alternatively, the mixture may be stirred at room temperature for at least 12 hr (overnight) without any deleterious effect on yield.

9. If the reaction is allowed to become warm, substantial protodesilylation of the product takes place to give 3-methyl-1-phenyl-1,3-butadiene. The aqueous workup should be carried out rapidly to minimize this side reaction. The use of hydrochloric acid has particular advantage since all of the salts dissolve facilitating the extractions.

10. Some residual salts precipitate during this operation, but do not pose any handling difficulty.

11. Gas chromatographic analysis (0.53-mm id x 10 m poly(dimethyl silicone) fused silica column, temperature programmed from 140°C to 220°C) indicates that this product is 98% pure, with <1% 3-methyl-1-phenyl-1,3-butadiene and 1-2% of a less volatile, unidentified component. The checkers could obtain a very pure product by normal vacuum distillation. They found the impurities to be higher boiling compounds.

12. This material has the following spectral data: IR cm^{-1} : 3068, 1593, 872, 853, 838; ^1H NMR δ : 0.01 (s, 9 H), 1.80 (br s, 2 H), 4.83 (br s, 1 H), 5.00 (d, 1 H, $J = 1$), 6.45 (d, 1 H, $J = 16$), 6.77 (d, 1 H, $J = 16$), 7.1-7.4 (m, 5 H); ^{13}C NMR δ : -1.2, 22.2, 114.8, 126.4, 127.3, 128.6, 128.7, 132.0, 137.4, 143.8; MS (m/e , %): 216 (40%), 73 (100%).

3. Discussion

Allylsilanes are exceptionally versatile compounds with a well-established function in organic synthesis.³ General methods for their preparation, then, are valuable. The method described here is effective for elaboration of esters to allylsilanes. The transformation is conceptually straightforward: twofold addition of a trimethylsilylmethyl metal species to the ester, followed by Peterson-type elimination from the resultant bis(trimethylsilylmethyl)carbinol, leads to the allylsilanes.

The Grignard reagent $\text{Me}_3\text{SiCH}_2\text{MgCl}$ has been used to effect this conversion with simple, unbranched esters, but the yields are only moderate (~50%) and the process fails completely for more sterically congested esters.⁴ In these cases, the α -silylketone intermediate resists further addition, instead suffering preferential enolization.⁵ The use of organocerium reagents to circumvent this difficulty has been developed by two groups.^{6,7} The reagent prepared from cerium(III) chloride and $\text{Me}_3\text{SiCH}_2\text{Li}$ is quite effective for conversion of acid chlorides to allylsilanes, but does not react efficiently with esters.⁶ Somewhat surprisingly in view of these results, a

mixture of cerium(III) chloride with $\text{Me}_3\text{SiCH}_2\text{MgCl}$ produces a powerful reagent for conversion of esters to allylsilanes in excellent yields.⁷ Some examples, for reactions carried out on a 1-mmol scale, are collected in the Table.⁷ Only the highly hindered methyl adamantanecarboxylate fails to react,

The protocol described above is a scaled-up modification of that reported earlier.⁷ The title compound has been prepared previously by a nickel-catalyzed cross-coupling,⁸ and by the organocerium/acid chloride route.⁶ The present procedure offers advantages in both convenience and yield compared to these other methods.

1. Department of Chemistry, University of Missouri-Columbia, MO 65211.
2. Whitmore, F. C.; Sommer, L. H. *J. Am. Chem. Soc.* **1946**, *68*, 481.
3. (a) Parnes, Z. N.; Bolestova, G. I. *Synthesis* **1984**, 991; (b) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.
4. (a) Petrov, A. D.; Ponomarenko, V. A.; Snegova, A. D. *Dokl. Akad. Nauk S.S.S.R.* **1957**, *112*, 79; *Chem. Abstr.* **1957**, *51*, 11239a; (b) Fleming, I.; Pearce, A. J. *Chem. Soc., Perkin Trans. I* **1981**, 251; (c) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *J. Chem. Soc., Chem. Commun.* **1982**, 1108; (d) Yamazaki, T.; Ishikawa, N. *Chem. Lett.* **1984**, 521.
5. Demuth, M. *Helv. Chim. Acta* **1978**, *61*, 3136.
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8. Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001.

Table

Ester	Allylsilane	Yield (%)
		95
		90 ^a
		95
		77
		92
		0 ^b

^aStarting material and product each a 1:1 mixture of diastereoisomers.^bStarting material recovered quantitatively.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

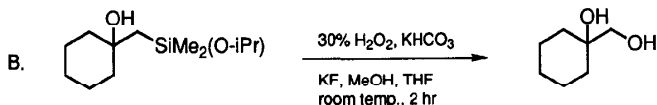
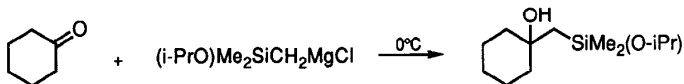
Trimethyl(2-methylene-4-phenyl-3-butenyl)silane. Silane, trimethyl(2-methylene-4-phenyl-3-butenyl)- (11); (80814-92-2)

Cerium(III) chloride heptahydrate: Cerium chloride heptahydrate (8); Cerium chloride (CeCl_3), heptahydrate (9); (18618-55-8)

Trimethylsilylmethylmagnesium chloride: Magnesium, [chloro[(trimethylsilyl)methyl]- (8,9); (13170-43-9)

Ethyl cinnamate: Cinnamic acid, ethyl ester (8), 2-Propenoic acid, 3-phenyl-, ethyl ester (9); (103-36-6)

**NUCLEOPHILIC HYDROXYMETHYLATION OF CARBONYL COMPOUNDS:
1-(HYDROXYMETHYL)CYCLOHEXANOL
(Cyclohexanemethanol, 1-hydroxy-)**



Submitted by Kohei Tamao, Neyoshi Ishida, Yoshihiko Ito, and Makoto Kumada.¹

Checked by Vinh D. Tran and Larry E. Overman.

1. Procedure

A. *1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol*. A 500-mL, three-necked flask is equipped with a pressure-equalizing dropping funnel, magnetic stirrer, three-way stopcock, and a reflux condenser connected with a nitrogen bubbler. The flask is charged with magnesium turnings (2.43 g, 100 mg-atm) which are dried under a rapid stream of nitrogen with a heat gun. After the flask is cooled to room temperature, the rate of nitrogen flow is reduced. Several mL of a solution of (isopropoxydimethylsilyl)methyl chloride (16.67 g, 100 mmol) (Note 1) in dry tetrahydrofuran (THF) (120 mL) (Note 2) and about 50 μL of 1,2-dibromoethane are added. The mixture is stirred at room temperature and within a few minutes an exothermic reaction starts. The remaining solution is added dropwise at room

temperature over ca. 45 min at such a rate as to maintain a gently exothermic reaction. After the addition is complete, the tan-grey mixture is refluxed for 0.5 hr and then cooled to 0°C with an ice bath. A solution of freshly distilled cyclohexanone (7.36 g, 75 mmol) in dry THF (30 mL) is added dropwise with stirring over 30 min. The resultant mixture is stirred at 0°C for another 30 min (Note 3) and then hydrolyzed by dropwise addition of an aqueous 10% solution of ammonium chloride (100 mL) at 0°C over 10 min. The organic layer is separated. The aqueous layer is extracted with four 40-mL portions of diethyl ether. The combined organic layer and extracts are washed once with aqueous saturated sodium chloride, dried over magnesium sulfate, filtered into a 500-mL round-bottomed flask and concentrated with a rotary evaporator below room temperature (Note 4) at water aspirator pressure. A colorless oil remains (Note 5).

B. 1-(Hydroxymethyl)cyclohexanol. The 500-mL, round-bottomed flask which contains the crude 1-[(isopropoxydimethylsilyl)methyl]cyclohexanol is equipped with a magnetic stirrer and a thermometer, and is kept open to air throughout the reaction. The flask is charged with tetrahydrofuran (75 mL), methanol (75 mL) (Note 6), potassium hydrogen carbonate (7.5 g 75 mmol), and potassium fluoride (8.7 g, 105 mmol) (Note 7). To the stirred mixture is added 30% hydrogen peroxide (28.0 mL, 247.5 mmol) in one portion at room temperature. A somewhat cloudy organic layer and a milky-white heavy inorganic layer result. After several minutes an exothermic reaction begins which is controlled by intermittent, brief cooling with a water bath to maintain the temperature at 40-50°C (Note 8). After about 30 min the exothermic reaction ceases. The mixture is then stirred at room temperature for 2 hr (Note 9). The remaining hydrogen peroxide is decomposed by careful dropwise addition (Note 10) of an aqueous 50% solution of sodium thiosulfate pentahydrate (ca. 30 mL) with stirring over 30 min, during which time the temperature is maintained near 30°C by intermittent cooling with an ice bath (Note 11). A negative starch-iodide test is

observed (Note 12). A white precipitate forms and diethyl ether (ca. 100 mL) is added to ensure further precipitation. The mixture is filtered with suction and the filter cake is washed with three 20-mL portions of diethyl ether. The combined filtrate and washes are concentrated with a rotary evaporator at 50°C/water aspirator pressure until much of the water has been removed. The remaining oil is diluted with diethyl ether (ca. 200 mL), transferred to a separatory funnel and washed with saturated aqueous sodium chloride solution to remove the remaining water. The organic layer is separated, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give a colorless solid. The solid is dissolved in a 10:1 mixture of hexane - ethyl acetate (75 mL) at reflux, and the hot solution is filtered. The filtrate is allowed to cool to room temperature and finally is kept at 0°C for 2 hr. The crystals are separated with suction, washed with cold hexane/ethyl acetate (10:1, 10 mL), and dried under high vacuum at room temperature. There is obtained 7.54 g (77%) of 1-(hydroxymethyl)cyclohexanol as white crystals, mp 76.0-76.2°C (Notes 13, 14).

2. Notes

1. (Isopropoxydimethylsilyl)methyl chloride² is readily prepared from (chlorodimethylsilyl)methyl chloride by treatment with isopropyl alcohol (1.1 equiv) and triethylamine (1.1 equiv) in diethyl ether at room temperature (0.5 hr) and then at reflux temperature (0.5 hr). After filtration of the white salt, the filtrate is washed successively once with water, twice with 0.1 N hydrochloric acid, once with an aqueous 10% solution of sodium hydrogen carbonate and once with water, then dried over sodium sulfate. Filtration and distillation give the product in 80% yield, bp 65-67°C/50 mm, as an air-stable, colorless liquid. The checkers used commercially available material purchased from Aldrich Chemical Company, Inc.

2. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen (*Caution: See Org. Synth., Coll., Vol. V 1973, 976 for a warning regarding the purification of tetrahydrofuran. The checkers employed THF that had been purified by distillation from sodium and benzophenone.*).

3. The color of the mixture lightened slightly.

4. Care must be taken not to raise the temperature since β -elimination of the β -hydroxysilane can result.

5. The remaining oil appeared as one spot on silica gel TLC, $R_f = 0.8$ (hexane/ethyl acetate 1:1), and showed the following ^1H NMR spectrum (CDCl_3 , 300 MHz) δ : 0.19 (s, 6 H $\text{Si}(\text{CH}_3)_2$), 1.01 (s, 2 H, CH_2Si), 1.20 (d, 6 H, $J = 6$, $\text{CH}(\text{CH}_3)_2$), 1.38-1.75 (m, 10 H, $(\text{CH}_2)_5$), 3.5 (s, OH), 4.04 (septet, 1 H, $J = 6$, $\text{OCH}(\text{CH}_3)_2$).

6. Commercial reagent grade THF and methanol are used without further purification.

7. Potassium fluoride of anhydrous grade was purchased from Nakarai Chemicals. Ltd. This must be weighed quickly because it is highly hygroscopic. The checkers used material purchased from Allied Chemical Company.

8. The oxidation is so exothermic that the temperature reaches 60-65°C in 10 min if no external cooling is applied.

9. Completion of the oxidation was confirmed by TLC on silica gel: R_f of the product diol is 0.4 (hexane/ethyl acetate 1:1).

10. Care must be taken not to add the thiosulfate solution in one portion; otherwise a violent, uncontrollable reaction might suddenly occur.

11. The reaction temperature should be monitored carefully. If it falls below 10°C, the cooling bath should be removed to allow the mixture to warm to ca. 30°C.

12. If the test is still positive, thiosulfate solution should be added until a negative test is attained. The checkers found EM Quant Peroxide Test Strips obtained from EM Science to be more sensitive than conventional KI-Starch test paper.

13. The reported melting point is 75-76°C.³

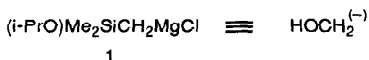
14. 1-(Hydroxymethyl)cyclohexanol exhibits the following spectral properties:

¹H NMR (300 MHz, CDCl₃) δ: 1.25-1.70 (broad m, 10 H, (CH₂)₅), 2.12 (s, 1 H, OH), 2.37 (t, 1 H, J = 6, OH), 3.45 (d, 2 H, J = 6, CH₂OH); IR (KBr) cm⁻¹: 3700-3020 (strong), 2920 (strong) 2845 (strong); Mass spectrum (24 eV): m/z (relative intensity) 130 (M⁺, 0.3), 99 (100), 81 (67); High resolution mass spectrum: Calcd for C₇H₁₄O₂, 130.0992; Found, 130.0969.

3. Discussion

This procedure for the preparation of 1-(hydroxymethyl)cyclohexanol is a modification of that reported by the submitters.⁴ While 1-(hydroxymethyl)cyclohexanol has been conventionally prepared from methylenecyclohexane by dihydroxylation^{5a} or from cyclohexanone in three steps through the cyanohydrin,^{5b} the present method consists of an alternative route from cyclohexanone via nucleophilic hydroxymethylation.

Although nucleophilic hydroxymethylating agents (hydroxymethyl anion synthons) or alkoxymethyl anions could be of great use in synthetic organic chemistry,⁶ only a few agents of this type have been developed so far. They include MeOH/TiCl₄/hν,⁷ Bu₃SnCH₂OH/BuLi,⁸ tert-BuOCH₂Li,⁹ HSiR₃/CO/Co₂(CO)₈,¹⁰ PhCH₂OCH₂Cl/SmI₂,¹¹ ArCO₂CH₂Li/LiAlH₄,¹² R₂BCH₂Li/[O],¹³ and (Me₃SiO)CH=C(OSiMe₃)₂.¹⁴ These methods are not as convenient or widely applicable as the method reported here. Two points deserve comment.

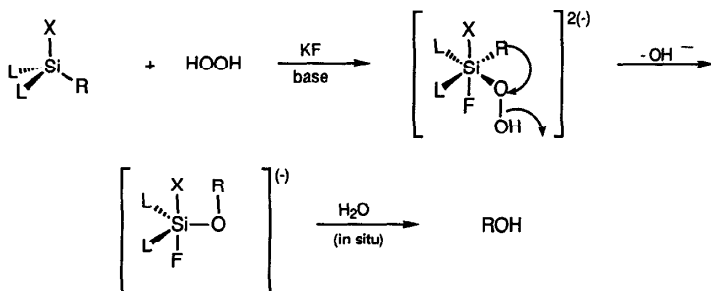


In addition to the (isopropoxydimethylsilyl)methyl Grignard reagent, (iso-PrO)Me₂SiCH₂MgCl (1), the (diisopropoxymethylsilyl)methyl counterpart, (iso-PrO)₂MeSiCH₂MgCl (2), has also been used as a nucleophilic hydroxymethylating agent.¹⁵ Despite labile alkoxy group(s) on silicon, the Grignard reagents are readily prepared in a normal manner in greater than 90% yields, and are sufficiently stable to be stored at room temperature for at least 2 days with little decrease in activity. The mono-isopropoxy Grignard reagent (1) is recommended as the reagent of first choice. Its precursor, (isopropoxydimethylsilyl)methyl chloride, is readily available at lower cost, and the reaction products, (iso-PrO)Me₂SiCH₂E, are more stable not only to aqueous work-up under weakly basic and acidic conditions, but also to silica gel chromatography.

The present method is based on the oxidative cleavage reaction of the silicon-carbon bond by hydrogen peroxide.¹⁶ The presence of at least one heteroatom on silicon is essential for the oxidative cleavage. Thus, the silicon-carbon bonds in hydro-, fluoro-, chloro-, alkoxy-, or amino-silanes are cleaved oxidatively to give the corresponding hydroxylated products. Although the oxidation may be performed in several ways, the following conditions (involving weak base and fluoride ion), may be the most efficient and most widely applicable: 30% H₂O₂ (1.2 equiv/Si-C bond), KHCO₃ (1 molar equiv), KF (2 molar equiv), MeOH/THF (1:1), room temperature. Under these conditions, the reaction usually occurs exothermically and is typically complete in several hours. Functional groups such as olefin, aldehyde, ketone, ester, amine, ether, ketal and tert-butyldimethylsiloxy groups, and furan, thiophene, and

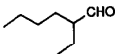
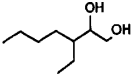

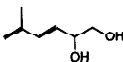

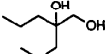



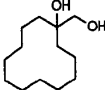
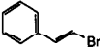
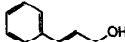
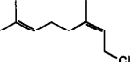
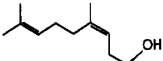
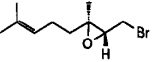
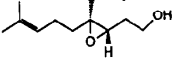
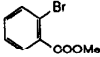



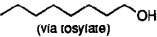


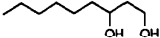
pyridine rings are stable under the oxidation conditions. The oxidation proceeds with complete retention of configuration at an sp^3 carbon. The oxidation has been considered to proceed through intramolecular migration of an organic group from silicon to the adjacent oxygen atom in penta- or hexacoordinate hydroperoxysilicon intermediates, as shown in Scheme 1 where X stands for a functional group. The oxidation has found a variety of synthetic applications.¹⁷

Scheme 1



Several representative examples of nucleophilic hydroxymethylation of aldehydes, ketones, organic halides, tosylates, and epoxides are summarized in Table I. The oxidation conditions given in the original literature are not necessarily optimum, and results may be improved by use of the oxidation method employed here. These results, summarized in Table I, demonstrate the general applicability of the silicon-based nucleophilic hydroxymethylation.

TABLE
Nucleophilic Hydroxymethylation of Aldehydes, Ketones,
Organic Halides, Alcohols, and Epoxides.^a

Starting Material	Product	Overall isolated yield (%)	Ref.
		67	4
		75	18
		86	4
		65	4
		63	4
		79	15
		87	15
		52	19
		86	15
		65	15
		67	20
		74	20

^a Introduction of the silylmethyl group into organic halides, tosylates, and epoxides is achieved by nickel-, palladium-, or copper-catalyzed cross-coupling reactions.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

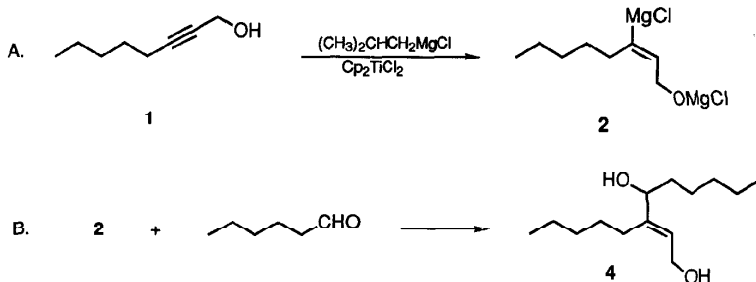
1-(Hydroxymethyl)cyclohexanol: Cyclohexanemethanol, 1-hydroxy- (8,9);
(15753-47-6)

(Isopropoxydimethylsilyl)methyl chloride: Silane, (chloromethyl)isopropoxydimethyl-
(9); (18171-11-4)

Cyclohexanone (8,9); (108-94-1)

HYDROMAGNESIATION REACTION OF PROPARGYLIC ALCOHOLS:

(E)-3-PENTYL-2-NONENE-1,4-DIOL FROM 2-OCTYN-1-OL



Submitted by Fumie Sato and Yuichi Kobayashi.¹

Checked by Zuliang Zhou and Ekkehard Winterfeldt.

1. Procedure

A. *The Grignard reagent 2.* A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL pressure equalizing dropping funnel, a glass stopper, and a two-way stopcock to which is attached a T-piece connected at one end to a supply of nitrogen, and at the other to an oil bubbler (Note 1). The flask is charged with a solution of isobutylmagnesium chloride in ether (320 mL, 0.75 M, 240 mmol) (Notes 2 and 3) and immersed in an ice-water bath. Titanocene dichloride (1.3 g, 5.2 mmol) (Note 4) is added at once and the resulting solution is allowed to stir at 0°C for 10 min. A solution of 2-octyn-1-ol (1) (13.2 g, 105 mmol) (Note 5) in ether (30 mL) (Note 3) is placed in the dropping funnel and added dropwise to the flask over 20 min at 0°C. The solution is stirred at room temperature for 4 hr to complete the reaction, affording Grignard reagent 2 (Notes 6, 7, and 8).

B. (E)-3-Pentyl-2-nonene-1,4-diol (4). Half the amount of the Grignard reagent **2** prepared according to Procedure A is diluted with ether (160 mL) and cooled in an ice-water bath to 0°C. A solution of hexanal (9.25 g, 92.5 mmol) (Note 9) dissolved in ether (30 mL) (Note 3) is added through the dropping funnel over 30 min with efficient stirring. After the addition is complete, the solution is stirred at 0-5°C for 2 hr and then poured into saturated ammonium chloride solution (300 mL). The mixture is stirred at 0°C for 1 hr. The resulting precipitate is removed by filtration through a pad of Celite (70 x 24 mm) under reduced pressure and the precipitate is washed with ethyl acetate (100 mL). The organic layer is separated and the aqueous phase is extracted with ethyl acetate (150 mL). The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to leave an oil which is purified by column chromatography on silica gel (Notes 10 and 11) to afford **4** (7.0-7.4 g, 59-62% yield) (Note 12).

2. Notes

1. Reactions A and B are carried out under a nitrogen atmosphere. The submitters used argon.

2. A solution of isobutylmagnesium chloride in ether was prepared using isobutyl chloride (13.8 g, 150 mmol), magnesium turnings (4.05 g, 165 mmol), and ether (175 mL) according to the procedure for the preparation of sec-butylmagnesium chloride reported by Gilman and Kirby.² The checkers found that this solution contained about 145 mmol of isobutylmagnesium chloride.

3. Ether and tetrahydrofuran were distilled from benzophenone ketyl under an argon atmosphere.

4. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc., and used without further purification.

5. Alcohol **1** was prepared according to the procedure of Rickards and Weiler³ and distilled under reduced pressure (102-108°C/15 mm) before use. This material is also commercially available from Farchan Laboratories, Inc. The checkers obtained it from Lancaster Chemical Co.

6. The checkers found that Grignard reagent **2** could not be obtained quantitatively although all of the isobutylmagnesium chloride had reacted. The end point of the reaction was determined by TLC analysis of a small amount of reaction mixture after hydrolysis. 2-Octyn-1-ol (**1**) and (Z)-2-octen-1-ol (**3**), have R_F values of 0.53 and 0.47, respectively (using Silica Gel 60 F₂₅₄ pre-coated TLC aluminum sheets and benzene-ethyl acetate (1:1) as developing agent). If the reaction is not complete, an additional amount of titanocene dichloride should be added to the solution which is cooled again to 0°C before the addition.

7. The submitters report that, if this solution is poured into 1 N hydrochloric acid and ice and worked up in the usual manner, (Z)-2-octen-1-ol (**3**) may be obtained in 86% yield by distillation, bp 97-101°C (12 mm). This product has the following spectra: IR (neat) cm^{-1} : 3290, 1457, 1014; ^1H NMR (90 MHz, CCl_4 , $(\text{CH}_3)_4\text{Si}$, D_2O) δ : 0.88 (t, 3 H, $J = 6$), 1.05-1.57 (m, 6 H), 1.85-2.22 (m, 2 H), 4.03 (d, 2 H, $J = 5$), 5.27-5.65 (m, 2 H).

8. The submitters report that, if this solution is concentrated, then dissolved in tetrahydrofuran and treated with methyl iodide, (Z)-3-methyl-2-octen-1-ol (**5**) may be obtained after silica gel chromatography using hexane-ether as eluent. This product has the following spectra: IR (neat) cm^{-1} : 3305, 1447, 1000; ^1H NMR (90 MHz, CCl_4 , $(\text{CH}_3)_4\text{Si}$, D_2O) δ : 0.88 (t, 3 H, $J = 6$), 1.1-1.6 (m, 6 H), 1.68 (s, 3 H), 1.9-2.2 (m, 2 H), 3.99 (d, 2 H, $J = 6$), 5.29 (t, 1 H, $J = 6$).

9. Hexanal was used as supplied by Tokyo Kasei Kogyo Co., Ltd. (Japan). The checkers obtained it from Aldrich Chemical Company, Inc.

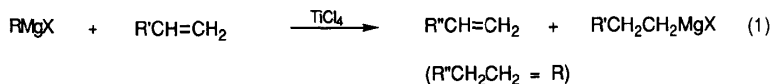
10. Silica gel (100-200 mesh) was purchased from Wako Pure Chemical Industries, LTD (Japan).

11. A silica gel column (225 g, 60 x 210 mm) is used with a mixture of benzene and ethyl acetate as an eluent [R_f value (benzene-ethyl acetate = 1:1): **3**, 0.47; **4**, 0.23]. Distillation of product **4** under reduced pressure caused partial decomposition (bp 120-155°C/0.25 mm).

12. Diol **4** has the following spectra: IR (neat) cm^{-1} : 3300, 1468, 1020; ^1H NMR (90 MHz, CDCl_3 , $(\text{CH}_3)_4\text{Si}$, D_2O) δ : 0.89 (t, 6 H, $J = 6$), 1.1-1.7 (m, 14 H), 1.9-2.2 (m, 4 H), 4.02 (m, 1 H), 4.20 (d, 2 H, $J = 6$), 5.63 (t, 1 H, $J = 6$). With D_2O exchange there is a change in the range of δ 1.9-2.2 (m, 2 H).

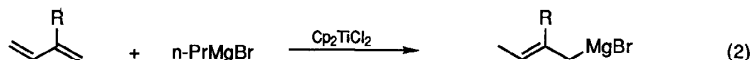
3. Discussion

In 1962 Cooper and Finkbeiner reported the titanium chloride (TiCl_4)-catalyzed exchange reaction of an alkyl Grignard reagent (RMgX) having β -hydrogen(s) with olefins (eq. 1).⁴ In this reaction, RMgX can be formally regarded as a source of HMgX which adds to the olefins, and hence this reaction is known as the hydromagnesiation reaction.

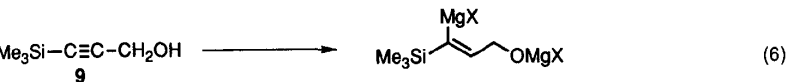
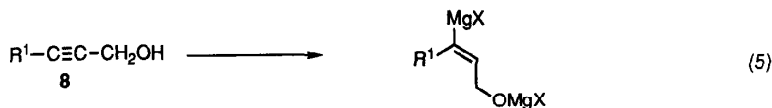
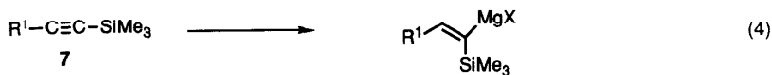
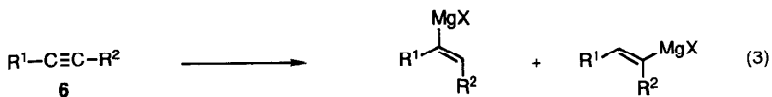


Since then, hydromagnesiation of other unsaturated hydrocarbons such as conjugated dienes and acetylenes has been investigated intensively.^{5,6} Hydromagnesiation of 2-alkyl substituted 1,3-butadienes has been shown to proceed

regiospecifically by using Cp_2TiCl_2 as a catalyst to afford the corresponding allylic Grignard reagent shown in eq. 2 quantitatively.⁷



Cp_2TiCl_2 -catalyzed hydromagnesiation of acetylenes with isobutyl Grignard reagents has also been shown to provide a convenient and practical method for preparation of various vinyl Grignard reagents. The acetylenes so far examined include 1,2-dialkylacetylenes **6** (eq. 3), 1-(trimethylsilyl)acetylenes **7** (eq. 4),⁸ propargyl alcohols **8** (eq. 5),⁹ and 3-(trimethylsilyl)propargyl alcohol (**9**) (eq. 6).¹⁰ Although the reaction occurs with low regioselectivity for unsymmetrical dialkylacetylenes **6**, high regioselectivity is attained in the case of **7**, **8**, and **9**. Acetylenes **6**, **7**, and **8** afford the corresponding vinylmagnesium halides in which HMgX adds in a syn pathway to the triple bond, while **9** affords the anti-addition product. In the latter case, hydromagnesiation follows the syn pathway to yield the corresponding (Z)-alkenyl Grignard reagent first, which, however, isomerizes rapidly under the reaction conditions to the (E)-alkenyl Grignard reagent. Since the hydromagnesiation reaction of **7**, **8**, and **9** proceeds highly regio- and stereoselectively, the reaction has become a powerful synthetic tool for utilization in organic syntheses. Some of the examples are given in the Table.



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

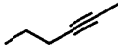
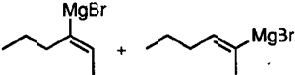
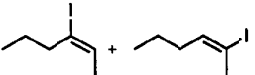
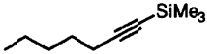
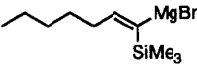

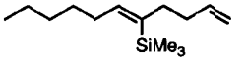

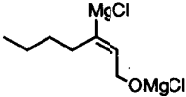
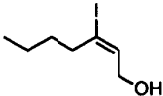
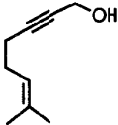
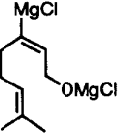
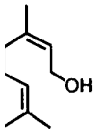
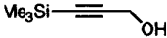
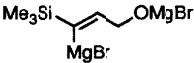
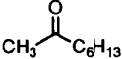
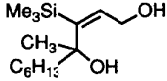
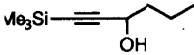
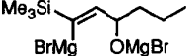
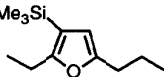
2-Octyn-1-ol (8,9); (20739-56-6)

Titanocene dichloride: Titanium, dichloro- π -cyclopentadienyl- (8);

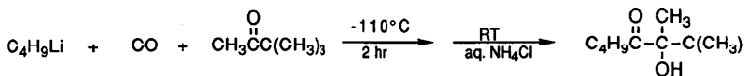
Titanium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1271-19-8)

Hexanal (8,9); (66-25-1)

Table

Starting Acetylene	i-BuMgX X	Vinylmagnesium Halide	Electrophile	Product	Yield %	Ref
	Br		I ₂	 42 : 58	70	8
	Br		 /CuI		86	11
	Cl		I ₂		78-86	9
	Cl		MeI		95	9
	Br				83	12
	Br		EtCN		86	13

**DIRECT NUCLEOPHILIC ACYLATION BY THE LOW TEMPERATURE,
IN SITU GENERATION OF ACYLLITHIUM REAGENTS; α -HYDROXY
KETONES FROM KETONES: 3-HYDROXY-2,2,3-TRIMETHYLOCTAN-
4-ONE FROM PINACOLONE
(4-Octanone, 3-hydroxy-2,2,3-trimethyl-)**



Submitted by Richard Hui and Dietmar Seyferth.¹

Checked by Hiroshi Koyano and Ryoji Noyori.

1. Procedure

A 2-L, three-necked flask was equipped with an overhead mechanical stirrer, a Claisen adapter which contained a low-temperature thermometer, and a no-air stopper which held a gas dispersion tube for the introduction of carbon monoxide (Note 1). The flask was charged with 400 mL each of tetrahydrofuran (THF) and diethyl ether, 100 mL of pentane, and pinacolone (7.92 g, 79.1 mmol) (Note 2). The reaction solution was cooled to -110°C (Notes 3 and 4) under an argon atmosphere and carbon monoxide (Note 5) was bubbled in for 30 min. Then a solution of butyllithium (2.53 N solution in pentane, 31.0 mL, 78.43 mmol) (Note 6) was added at 0.6-1.0 mL/min by means of a syringe pump (Note 7). The reaction mixture was orange after the addition had been completed. The reaction mixture was stirred at -110°C for 2 hr while the carbon monoxide stream was continued. The liquid nitrogen Dewar was removed, and the reaction mixture was allowed to warm to room temperature over the course of 1.5 hr, during which time the color changed to yellow.

The reaction mixture subsequently was quenched by the addition of 300 mL of saturated ammonium chloride solution, which resulted in a light yellow organic layer and a clear, colorless aqueous phase. The aqueous layer was separated and washed twice with 100 mL of pentane. The organic layers were combined, dried over anhydrous magnesium sulfate and filtered. The solvents were removed by fractional distillation (9" Vigreux column). The residue was distilled through a 7-cm jacketed column to give 9.7-10.8 g (67-73%) of 3-hydroxy-2,2,3-trimethyloctan-4-one, 97% pure by GLC, bp 120-122°C (30 mm), and n_D^{20} 1.442 (Note 8).

2. Notes

1. All glassware was dried for 15 hr in an oven at ca. 110°C and assembled while still warm.

2. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Pentane was distilled from lithium aluminum hydride and stored in bottles under a positive pressure of nitrogen. Pinacolone was distilled from potassium carbonate prior to use, bp 106°C (760 mm).

3. Total immersion type low temperature pentane thermometers (Kessler) were used to measure the temperature in the partial immersion mode. The readings are usually 7-8°C higher compared to the actual temperature under our reaction conditions. The temperatures reported here are all corrected by subtracting 7°C from the thermometer readings. The checkers used a Delta MC-20R digital thermometer (Sato Keiryoki Co., Japan). Temperature control is very important to obtain a satisfactory yield.

4. The temperature was controlled by moving a liquid nitrogen-filled Dewar flask up and down with a lab jack.

5. Carbon monoxide, purchased from Matheson Gas Products or Nihon Sanso Co., was used without further purification.

6. Butyllithium in pentane was purchased from Alfa Products, Morton/Thiokol Inc. and was titrated by the method of Gilman and Cartledge.^{2a} The checkers used a 1.56 N hexane solution purchased from Mitsuwa Chemical Co. after titration by the Kotron-Baclawski procedure.^{2b}

7. Orion Research Inc., Model 341 was used. Alternatively, if a syringe pump is not available, the organolithium solution may be added manually by syringe, very slowly and at a reasonably constant rate.

8. GLC conditions were as follows: 2 m x 5-mm glass column packed with 20% silicone SE-30 on chromosorb W AW; gas flow: 0.8 kg/cm²; temperature program 100-275°C at 6°C per minute; retention times: n-C₉H₂₀, 4.9 min; 3-hydroxy-2,2,3-trimethyloctan-4-one, 12.5 min. Spectral properties of the product are as follows: IR (thin film, NaCl) cm⁻¹: 3350-3580 (br, s, v-OH), 2985 (s), 2872 (m), 1695 (s, v C=O), 1480 (m), 1465 (s), 1462 (s), 1395 (s), 1220 (m), 1170 (m), 1125 (s), 1040 (s), 990 (m), 910 (m); ¹H NMR (270 MHz, CDCl₃) δ: 0.92 (t, 3 H, J = 7.3, CH₂-CH₃), 0.97 (s, 9 H, C(CH₃)₃), 1.33 (tq, 2 H, J = 7.3, 7.3, CH₂=CH₃), 1.34 (s, 3 H, CH₃), 1.60 (tt, 2 H, J = 7.6, 7.6, CH₂CH₂C(O)), 2.52 (dt, 1 H, J = 15.2, 7.6, a proton of CH₂C(O)), 2.60 (dt, 1 H, J = 15.2, 7.0, a proton of CH₂C(O)), 3.04 (s, 1 H, OH).

3. Discussion

In situ generated acyllithium reagents not only can acylate ketones, but also can acylate aldehydes,³ esters,⁴ lactones,⁵ isocyanates and isothiocyanates,⁶ carbodiimides,⁷ carbon disulfide and carbonyl sulfide,⁸ organic disulfides,⁹ and trialkylchlorosilanes.¹⁰ For reviews, see references 11 and 12. This direct, nucleophilic acylation procedure, when applicable, makes unnecessary the usually

applied method of "masked acyl anion equivalents" for nucleophilic acylation.¹³ The present procedure finds only very limited applicability in the case of aryllithium/CO systems,¹⁴ but seems to be generally applicable to alkyllithium systems.

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Appendix


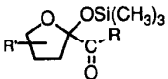
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-Hydroxy-2,2,3-trimethyl-4-octanone: 4-Octanone, 3-hydroxy-2,2,3-trimethyl- (11);
(85083-71-2)

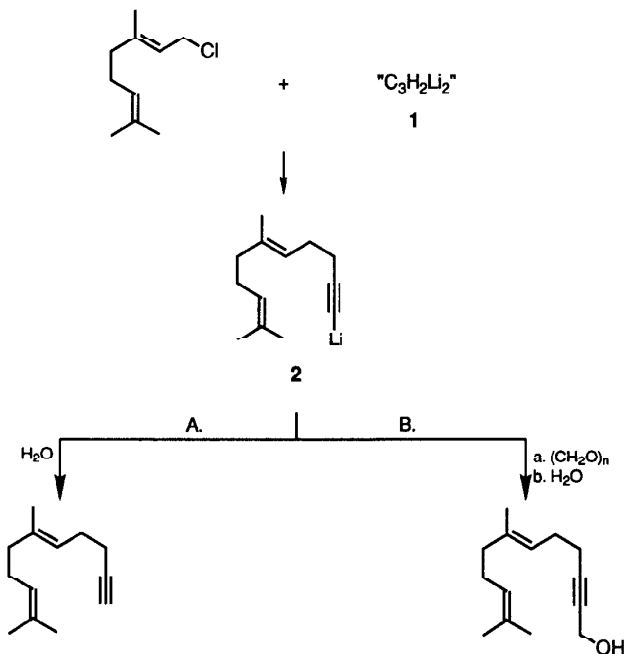
Pinacolone: 2-Butanone, 3,3-dimethyl- (8,9); (75-97-8)

Table

Low Temperature, in situ, Direct Nucleophilic Acylation with the RLi/CO Reagent

Electrophile	Quench Reagent	Product	Reference
$(\text{CH}_3)_3\text{SiCl}$	H_2O	$(\text{CH}_3)_3\text{Si}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R}$	10
$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R}''$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{C}(\text{OH})\text{R}'\text{R}''$	3,4
$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OR}''$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R}'$	4
$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NR}''_2$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R}'$	12
$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{SR}''$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R}'$	9
$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{H}$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}(\text{OH})\text{R}'$	3
	$(\text{CH}_3)_3\text{SiCl}$		5
$\text{R}'\text{SSR}'$	H_2O	$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{SR}'' + \text{RSH}$	9
$(\text{CH}_2)_n \begin{smallmatrix} \text{S} \\ \text{S} \end{smallmatrix}$ $n = 4,5$	CH_3I	$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{S}(\text{CH}_2)_n\text{SCH}_3$	9
S_8	CH_3I	$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{SCH}_3$	9
COS	CH_3I	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{SCH}_3$	8
CS_2	CH_3I	$\text{R}'-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{SCH}_3$	8
$\text{R}'\text{NCO}$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NHR}'$	6
$\text{R}'\text{NCS}$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NHR}'$	6
	CH_3I	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{SCH}_3$	6
$\text{R}'\text{N}=\text{C}=\text{NR}'$	H_2O	$\text{R}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NHR}'$	7
$\text{Fe}(\text{CO})_5$		$(\text{OC})_4\text{Fe}=\overset{\text{O}^-}{\underset{\text{O}}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R} \quad (\text{CH}_3)_4\text{N}^+$ (R = tert-Bu)	15

**PROPARGYLATION OF ALKYL HALIDES: SYNTHESIS OF
(E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE AND
(E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL
(5,9-Undecadien-1-yne, 6,10-dimethyl-, (E)-) and
(6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (E)-)**



Submitted by John Hooz,^{1*} Jorge Cabezas,² Sergio Musmanni,² and Jose Calzada.^{2*}

Checked by Hanno Wild, Andreas Weier, and Larry E. Overman.

1. Procedure

Caution! Allene and ethyl ether are highly volatile and flammable. Paraformaldehyde is a noxious material. The entire operation should be conducted in an efficient fume hood.

A. *(E)-6,10-Dimethyl-5,9-undecadien-1-yne.* An oven-dried (Note 1), 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar (Note 2), a 250-mL pressure-equalizing addition funnel capped by a rubber septum (Note 3), a dry ice condenser capped by a rubber septum, and a rubber septum (capping the central neck) bearing a stainless steel cannula which serves as an argon inlet. The flask is charged with 190 mL of anhydrous ethyl ether (Note 4) and cooled to ca. -78°C using a dry ice-acetone bath. On a separate assembly (Note 5), allene gas (d at -40°C = 0.67 g/mL) from a compressed gas cylinder (Note 6) is condensed into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry ice condenser (containing a slurry of dry ice-acetone) and cooled to -78°C with a bath of dry ice-acetone (Note 7). After 22.5 mL (375 mmol) of liquid allene has been collected, the adapter and condenser are removed and the graduated cylinder is capped with a rubber septum through which is inserted a cannula. The other end of this cannula is inserted through the rubber septum on the central neck to reach just below the surface of the cooled solvent. The allene is then transferred to the reaction vessel by removing the cylinder from the cooling bath. The temperature of the reaction vessel is maintained at -78°C , and a solution of 190 mL of 1.37 M butyllithium (260 mmol) in hexane (Note 8) is added dropwise over 1 hr through the addition funnel which is then rinsed with 5 mL of dry ether. The reaction mixture is allowed to warm gradually (over ca. 30 min) to -15°C and the white precipitate that forms is stirred an additional 15 min under an argon atmosphere. A solution of 12.9 g (75 mmol) of geranyl chloride (Note 9) in 40 mL of

dry ether is added dropwise over 30 min through the addition funnel while maintaining the temperature at -15°C . Then the stirred mixture is allowed to warm to room temperature over 1 hr (Note 10). The resulting white suspension containing the lithium acetylide **2** is carefully poured into 450 mL of ice water slurry, the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined extracts are dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is distilled at atmospheric pressure using a 25-cm Vigreux column. The residue is distilled through a short-path distillation apparatus to afford 10.5-11.2 g (79-89% yield) of (E)-6,10-dimethyl-5,9-undecadien-1-yne, bp $103-107^{\circ}\text{C}$ (10 mm) (Note 11).

B. (E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol. To the suspension containing the acetylide intermediate **2**, as prepared in part A, is added 14 g (460 mmol) of paraformaldehyde (Note 12) in portions (Note 13) over 10 min (Note 14). After stirring the mixture for 24 hr, the resulting suspension is poured into 450 mL of ice-cold water (Note 15), the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined organic extracts are dried over magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed at room temperature on a rotary evaporator. The residue is distilled through a short-path distillation apparatus to provide a forerun of 2-butyne-1-ol (bp $42-46^{\circ}\text{C}$, 6 mm), followed by 10.5 g (68% yield) of (E)-7,11-dimethyl-6,10-dodecadien-2-yn-1-ol as a colorless liquid, bp $120-124^{\circ}\text{C}$ (0.5 mm) (Note 16).

2. Notes

1. All glassware is dried in an oven at 125°C and assembled while warm.
2. Although the reaction mixture will become heterogeneous, mechanical stirring is unnecessary on this scale.

3. A stainless steel cannula inserted through this septum is connected by means of tygon tubing to a mercury bubbler.

4. Ethyl ether is freshly distilled from the sodium ketyl of benzophenone.

5. This is an adaptation of the method used to condense methyl chloride, illustrated in Figure 1 of an *Organic Syntheses* procedure (Lusch, M. J.; Phillips, W. V.; Sieloff, R. F.; Nomura, G. S.; House, H. O. *Org. Synth., Coll. Vol. 7*, 1990, 347).

6. The submitters used allene purchased from Matheson Gas Products, Inc. The checkers found that an old lecture bottle of allene from this source gave unsatisfactory results, affording a crude product that contained up to 20% of unchanged geranyl chloride. Other lecture bottles of allene from Matheson or Pfaltz and Bauer were satisfactory.

7. All temperatures recorded are external bath temperatures.

8. A solution of butyllithium in hexane was purchased from Foote Mineral Company. Before use the concentration is determined by titration according to the procedure of Watson and Eastham.³

9. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, Inc., with carbon tetrachloride and triphenylphosphine according to an *Organic Syntheses* procedure.⁴

10. If dienyne product containing less than 1% of geranyl chloride is required, the checkers suggest the following treatment at this point to destroy any remaining geranyl chloride: The addition funnel is removed and a gentle stream of argon is bubbled through the stirred reaction mixture for 15 min to remove oxoallene. Additional butyllithium (40 mmol in hexane) is added and the resulting mixture is stirred for 3 hr at room temperature prior to hydrolytic work up. If this modification is employed the subsequent hydrolysis step should be done slowly. The Erlenmeyer flask (1 L) containing the ice/water mixture is best cooled externally with an ice bath during the hydrolysis.

The checkers also report that (E)-6,10-dimethyl-5,9-undecadien-1-yne containing < 1% geranyl chloride is produced in 78-90% yield when 2.0 mmol of butyllithium per mmol of allene is employed.

11. Capillary GC analysis of the product using a 25-m fused silica DB-5 column shows the presence of 5% geranyl chloride which is eluted at a slightly shorter retention time than the enyne product. Similar analysis of the product produced (in 89% yield) by the modification reported in Note 10 showed that the product was > 96% pure and contained < 1% of geranyl chloride. Spectral properties for (E)-6,10-dimethyl-5,9-undecadien-1-yne are: IR (thin film) cm^{-1} : 3312, 2119, 1665; ^1H NMR (300 MHz, CDCl_3) δ : 1.58 (s, 3 H), 1.60 (s, 3 H), 1.66 (s, 3 H), 1.97-2.14 (m, 4 H), 2.22 (narrow m, 4 H), 5.11 (m, 2 H), 5.19 (m, 1 H).

12. Paraformaldehyde is dried over P_2O_5 in a vacuum desiccator for 24 hr prior to use.

13. The dropping funnel is removed and replaced by a 250-mL Erlenmeyer flask containing the paraformaldehyde. This is connected to the reaction vessel by rubber tubing. The cannula previously attached to the mercury bubbler is inserted through the septum of the dry ice condenser.

14. The reaction with paraformaldehyde has an induction period of approximately 7-10 min, when the solvent suddenly begins to boil. The dry ice condenser should be kept charged with dry ice-acetone to avoid loss of solvent.

15. In some runs the checkers found that the slurry became too thick to stir. In these cases, the ice-cold water (450 mL) was added to the reaction flask while stirring the solid mass with a large spatula. The final yield of the alcohol product was similar in these runs. Alternatively the reaction flask can be mechanically stirred.

16. The purity of the product was determined to be 92-94% by capillary GLC analysis using a fused silica 25-m x DB-5 column, 70-280°C (10°C/min). The spectral properties of the product are as follows: IR (thin film) cm^{-1} : 3334, 2287, 2224, 1670

and 1020; ^1H NMR (500 MHz, CDCl_3) δ : 1.50 (t, 1 H, $J = 10.8$), 1.60 (s, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.99 (m, 2 H), 2.07 (m, 2 H), 2.22 (narrow m, 4 H), 4.25 (d, 2H, $J = 10.8$), 5.09 (m, 1 H), 5.16 (m, 1 H). Vinylic signals for minor impurities are apparent at δ 4.7-4.9.

3. Discussion

The highly-useful three-carbon homologation, $\text{RX} \rightarrow \text{RCH}_2\text{C}\equiv\text{CH}$, often employed in isoprenoid-related syntheses (e.g., sirenin,⁵ C_{18} -Cecropia juvenile hormone,⁶ 16,17-dehydroprogesterone⁷) is frequently difficult to accomplish cleanly because of the tendency of ambident propargylic nucleophiles, $\text{R-C}\equiv\text{C-CH}_2\text{M}$, **3**, to produce troublesome mixtures of both the allenic and acetylenic products.^{8,9,10} Propargyl alanates **3** [$\text{M}=\text{Al}(\text{i-C}_4\text{H}_9)_3$], for example, couple with allyl bromide to produce mainly the corresponding allene (< 4% acetylene), whereas the analogous borate complex **3** [$\text{M}=\text{B}(\text{sec-C}_4\text{H}_9)_3$] produces an 83:17 mixture of the corresponding allene:acetylene.¹¹ The "propargyl" Grignard reagent¹² also couples with allylic halides^{7,13,14} to produce acetylenic-allenic mixtures, for which a separation procedure has been developed based on trimethylsilylation of the crude product mixture.¹³ An indirect procedure employing lithio-1-trimethylsilylpropyne initially produces the trimethylsilyl-protected acetylene (50-55%), from which the required homologated alkyne is liberated by reaction with ethanolic silver nitrate followed by sodium cyanide.¹⁵ 1,3-Dilithiopropyne in either tetramethylethylenediamine or 1,4-diazabicyclo[2.2.2]octane is reported to couple with simple halides¹⁶ to form acetylenes in moderate yield, although it fails to couple cleanly with allylic halides.¹⁷

The present procedure, based on the controlled lithiation of allene, produces the operational equivalent of a propargyl dianion **1** ($\text{C}_3\text{H}_2\text{Li}_2$), and provides a convenient single-step route to propargylated derivatives. Lithiation of allene is

deceptively complex, and the extent of metalation (i.e., mono-, di-, tri-, tetra-) and the regiochemical outcome of subsequent alkylation (allenic vs. acetylenic) is highly dependent on reaction conditions. Metalation by butyllithium (1 equiv, THF, -70°C) followed by alkylation with octyl iodide produced an 87:13 mixture of the corresponding allene and acetylene,¹⁸ whereas an allene:C₄H₉Li ratio of 1:2 (THF, -50°C) followed by trimethylsilylation, produced a mixture comprised of mono-, di-, tri-, and tetra-silylated products.¹⁹ In the current procedure, the solvent ratio (v/v) of ether:hexane of 1:1, as well as the stoichiometry and temperature, were empirically determined, and under these conditions there was no detectable evidence (NMR, GLPC) of isomeric allene formation in any of the alkylations examined, either for simple or allylic halides.²⁰ An additional advantage is that the initially-formed lithium acetylide intermediate (e.g., **2**) may be further transformed to other useful functional derivatives in situ, as illustrated by the hydroxymethylation procedure.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(E)-6,10-Dimethyl-5,9-undecadien-1-yne: 5,9-undecadien-1-yne, 6,10-dimethyl-,

(E)- (8,9); (22850-55-1)

(E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol: 6,10-Dodecadien-2-yn-1-ol,

7,11-dimethyl-, (E)- (8,9); (16933-56-5)

Allene (8); 1,2-Propadiene (9); (463-49-0)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Geranyl chloride: 2,6-Octadiene, 1-chloro-3,7-dimethyl-, (E)- (8,9); (5389-87-7)

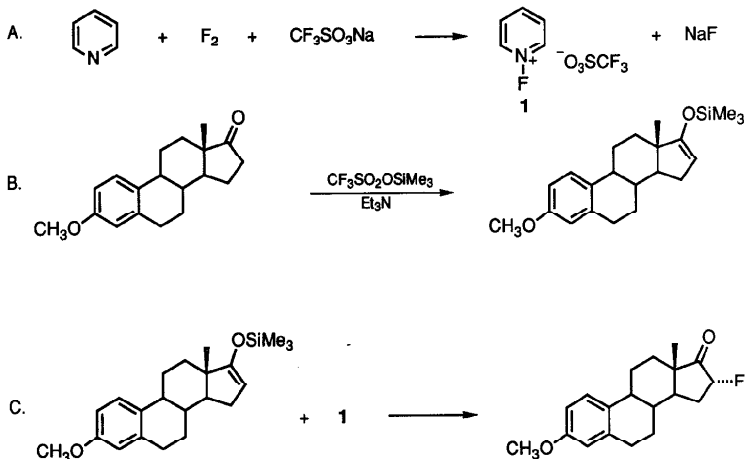
Paraformaldehyde $(\text{CH}_2\text{O})_n$: Poly(oxymethylene) (8,9); (9002-81-7) [Supplied by Alfa]

or Paraformaldehyde $(\text{CH}_2\text{O})_x$ (9); (30525-89-4) [Supplied by Aldrich, Fischer, Fluka]

N-FLUOROPYRIDINIUM TRIFLATE:

AN ELECTROPHILIC FLUORINATING AGENT

(Pyridinium, 1-fluoro-, salt with trifluoromethanesulfonic acid (1:1))



Submitted by Teruo Umemoto,^{1a} Kyoichi Tomita,^{1a,b} and Kosuke Kawada.^{1a,b}

Checked by Shlomo Rozen and Bruce E. Smart.

1. Procedure

Caution! Molecular fluorine is a very toxic and corrosive gas. The following reaction should be carried out in an efficient fume hood, and the experimenter should be familiar with the precautions necessary for safe handling of fluorine.² Since molecular fluorine diluted with an inert gas is much safer to handle than pure fluorine,

the use of a fluorine/nitrogen mixture comprising no more than 20% fluorine is recommended.

A. *N*-Fluoropyridinium triflate (1). The reaction is carried out in the apparatus shown in Figure 1. The pressure regulator on the cylinder containing a mixture of 20% fluorine/80% nitrogen (Note 1), and the pressure gauge and flowmeter on the fluorine line are specifically designed for fluorine service (Note 2). The fluorine and nitrogen cylinders, pressure regulators, flowmeters, valves, and filters are connected with stainless steel tubing. The Pyrex glass reaction vessel is connected to the metal tubing via Viton® tubing, and the fluorine gas is introduced into the vessel through a Pyrex glass tube (7 mm o.d.). The gas outlet from the reaction vessel is connected to a granular alumina trap which consumes molecular fluorine.

The 300-mL, round-bottomed reaction flask is charged with 4.74 g (0.06 mol) of pyridine (Note 3), 10.3 g (0.06 mol) of sodium triflate (Note 4), and 80 mL of dry acetonitrile (Note 5). The system is purged with nitrogen, and the reaction mixture is chilled and maintained at -40°C. The flow of dilute fluorine is started, and the flow rates from the nitrogen and fluorine cylinders are adjusted to introduce a 10% fluorine/90% nitrogen mixture at a rate of 90 mL/min just above the surface of the rapidly stirred solution (Note 6). When a total of 2.7 L of fluorine (0.12 mol) is introduced (Note 7), the flow of fluorine is discontinued and nitrogen only is flowed through the system at a rate of 45 mL/min for 30 min while keeping the reaction mixture at -40°C. The reaction mixture is then warmed to room temperature and filtered through a pad of Celite to remove the sodium fluoride. The filtrate is concentrated to dryness with a rotary evaporator without heating. The crystalline residue is washed with 30 mL of dry ethyl acetate to give 11.0-12.0 g (74-81%) of crude product, mp 178-181°C. The crude material is dissolved in 18 mL of dry acetonitrile at room temperature, and 36 mL of dry diethyl ether is added. The

precipitated crystals are collected by filtration under nitrogen (Note 8) to give 10.0-10.3 g (68-70%) of pure N-fluoropyridinium triflate, mp 182°C (Notes 9, 10, and 11).

B. 3-Methoxy-17-trimethylsiloxy-1,3,5(10),16-estratetraene. A 125-mL, two-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer is purged with argon and charged with 6.8 g (0.024 mol) of estrone 3-methyl ether (Note 12), 50 mL of dry benzene, and 4.0 mL (2.9 g, 0.029 mol) of triethylamine. The solution is stirred, 4.9 mL (5.6 g, 0.025 mol) of trimethylsilyl triflate (Note 13) is added through a syringe, and the mixture is refluxed for 1.5 hr. The reaction mixture is allowed to cool to room temperature, whereupon it separates into two layers. Dry hexane (40 mL) is added, and the upper hexane benzene layer is separated, washed successively with saturated sodium bicarbonate and water, and then dried over magnesium sulfate. The drying agent is removed by filtration, and the filtrate is transferred to a 125-mL, round-bottomed, tared flask. The solution is evaporated to a constant weight with a rotary evaporator, initially at water-aspirator pressure and then at 0.5-1 mm, to leave 8.6 g (100%) of pale yellow enol trimethylsilyl ether. This material is used immediately in Part C without purification (Note 14).

C. 16 α -Fluoro-3-methoxy-1,3,5(10)-estratrien-17-one (16 α -fluoroestrone 3-methyl ether). The 125-mL, round-bottomed flask containing the enol silyl ether from Part B is purged with argon, and 50 mL of dry dichloromethane is added. N-Fluoropyridinium triflate (1) (6.5 g, 0.026 mol) is added in one portion, and the mixture is stirred at 20-25°C for 8 hr (Note 15). The reaction mixture is poured into water and extracted with three 60-mL portions of dichloromethane. The combined organic extracts are washed with saturated sodium bicarbonate and then with water, and dried over magnesium sulfate. The drying agent is removed by filtration and the solution is evaporated to dryness with a rotary evaporator. The resulting pale yellow solid is column-chromatographed on silica gel (250 g, 60 cm x 4.5 cm column) using dichloromethane eluent (Note 16) to give 950 mg (14%) of estrone 3-methyl ether

starting material and 4.8 g (66%) of 16 α -fluoroestrone 3-methyl ether as a colorless solid, mp 157°C (Notes 17, 18, 19).

2. Notes

1. A cylinder containing 20% fluorine/80% nitrogen was obtained from Air Products & Chemicals, Inc.

2. The checkers used a Matheson model B15F-679 single-stage pressure regulator, a model 63-5512 pressure gauge, and a model 7825 flowmeter. Information on equipment designed to handle fluorine can be found in the bulletin Tech-Brief TB-115, published by Matheson Gas Products.

3. Anhydrous pyridine (99+%) packaged under nitrogen was purchased from Aldrich Chemical Company, Inc., and used without further purification.

4. Sodium trifluoromethanesulfonate (triflate) was prepared from trifluoromethanesulfonic acid (Aldrich Chemical Company, Inc.) as follows: A solution of 26.5 g (0.66 mol) of sodium hydroxide in 50 mL of water was added dropwise to 100 g (0.67 mol) of triflic acid chilled in an ice bath. The solution was concentrated to dryness with a rotary evaporator, and the residual solid was recrystallized from 65 mL of acetonitrile. The collected solid was dried at 80°C under vacuum for 24 hr to give 90 g of pure sodium triflate.

5. Acetonitrile was distilled from calcium hydride under nitrogen immediately before use.

6. A powerful magnetic stirrer was used to obtain a stirring rate of about 80 r.p.s. The checkers also used a VIBRO-Mixer E1 (Chemapec, Inc.). The checkers found that the yield was unaffected if the fluorine is introduced below rather than above the surface of the solution.

7. A substantial excess of fluorine over the theoretical, equimolar amount is needed to complete the reaction because of the low solubility of fluorine. The amount of fluorine required can vary depending upon the scale of reaction, the flow rate, and the efficiency of mixing.

8. The submitters carried out the filtration procedure in air. The procedure in wet air should be avoided.

9. The submitters report obtaining 13.2 g of crude product, mp 181-184°C, and 12.0 g (81%) of recrystallized material, mp 185-187°C.

10. The product obtained by the checkers is pure by NMR analyses. N-Fluoropyridinium triflate (**1**) has the following spectral properties: ^1H NMR (CD_3CN) δ : 8.32 (m, 2 H), 8.77 (m, 1 H), 9.33 (dd, 2 H, $J = 16, 7$); ^{19}F NMR (CD_3CN) δ : 48.8 (bs, 1 F, N-F), -77.6 (s, 3 F, CF_3); IR (Nujol on NaCl plate) cm^{-1} : 3140 (s), 3120 (s), 3080 (s), 3050 (s), 1600 (m), 1485 (s), 1475 (s), 1330 (w), 1270 (s), 1250 (s), 1220 (s), 1200 (s), 1175 (s), 1160 (s), 1090 (m), 1055 (w), 1020 (s), 805 (m), 770 (s), 755 (m), 630 (s).

11. N-Fluoropyridinium triflate is stable and can be stored indefinitely under a dry atmosphere. It slowly decomposes in water. The submitters report that it has a half-life of 13 days in D_2O at room temperature.

12. Estrone 3-methyl ether (3-methoxyestra-1,3,5(10)-trien-17-one) was purchased from Sigma Chemical Company.

13. Trimethylsilyl triflate was obtained from Aldrich Chemical Company, Inc., and used without further purification.

14. The product exhibits the following partial spectral data: ^1H NMR (CDCl_3) δ : 0.21 (s, 9 H, CH_3Si), 0.87 (s, 3 H, 18- CH_3), 3.77 (s, 3 H, OCH_3), 4.53 (m, 1 H, 16-H). *This silyl enol ether is sensitive to hydrolysis, and the submitters recommend that it be isolated in the same flask which is used for its subsequent reaction in Part C.*

15. Crystals of **1** gradually disappear as the reaction proceeds, and the mixture turns orange and finally becomes homogeneous when the reaction is completed.

16. Each fraction was monitored by thin-layer chromatography on silica gel (Merck Silica Gel 60 F-254). The R_f values (dichloromethane) of the product and starting estrone 3-methyl ether are 0.53 and 0.40, respectively.

17. The product has the following characteristic spectral properties: ^1H NMR (360 MHz, CDCl_3) δ : 0.95 (s, 3 H, 18- CH_3), 3.77 (s, 3 H, OCH_3), 5.13 (dd, 1 H, $J = 50.6$, 7.3, 16 β -H), 6.64 (d, 1 H, $J = 2.7$, 4-H), 6.72 (dd, 1 H, $J = 8.6$, 2.7, 2-H), 7.19 (d, 1 H, $J = 8.6$, 1-H); ^{19}F NMR (CDCl_3) δ : -192.7 (m); IR (KBr) cm^{-1} : 2900, 2850, 1750, 1600, 1500, 1460, 1440, 1310, 1240, 1030, 1000; MS m/e (relative intensity) 304 (2.7), 303 (21.5), 302 (M^+) (100), 301 (3.7).

18. The product contains about 4% of the 16 β -fluoroestrone epimer; ^1H NMR (360 MHz, CDCl_3) δ : 4.76 (dt, $J = 50$, 8; 16 α -H); ^{19}F NMR (CDCl_3) δ : -185.3 (dd, $J = 50$, 22; 16 β -F).

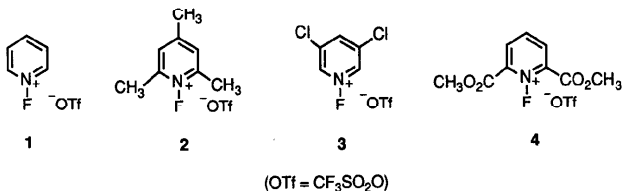
19. Identical yields of recovered starting material and product were obtained when Parts B and C were run on 2.5 times the scale. The submitters report obtaining a 78% yield of product, mp 145-149°C (recrystallized from ethyl acetate/hexane after chromatography) containing a small but unspecified amount of its epimer, along with 11% recovered starting material and 12% 2-pyridyl triflate, which is a decomposition product of 1. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{O}_2\text{F}$: C, 75.47; H, 7.00. Found: C, 75.52; H, 7.01.

3. Discussion

Electrophilic fluorinating agents such as F_2 ,³ CF_3OF ,⁴ FCIO_3 ,⁵ CF_3COOF ,⁶ CH_3COOF ,⁷ XeF_2 ,⁸ and CsSO_4F ⁹ require the use of special equipment and techniques because of their explosive, toxic, unstable, or hygroscopic nature. N-Fluoroperfluoropiperidine,¹⁰ N-fluoropyridone,¹¹ and N-fluoro-N-alkyltoluene-sulfonamides¹² are easy to handle, but their low reactivity limits the scope of their

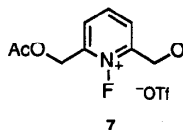
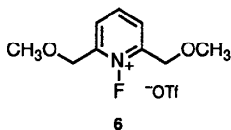
applications. More reactive N-fluoroperfluorosulfonamides¹³ have been recently reported as particularly useful reagents for aromatic fluorination.

N-Fluoropyridinium trifluoromethanesulfonate (triflate) and its derivatives are effective, stable fluorinating agents with varying degrees of fluorinating power.¹⁴ The procedure given here represents a general method for preparing substituted N-fluoropyridinium triflates. Triflates **2-4** can be made in good yields in the same manner as **1**, although instead of sodium triflate, potassium triflate is required for **2**, and lithium triflate for **3** and **4**.



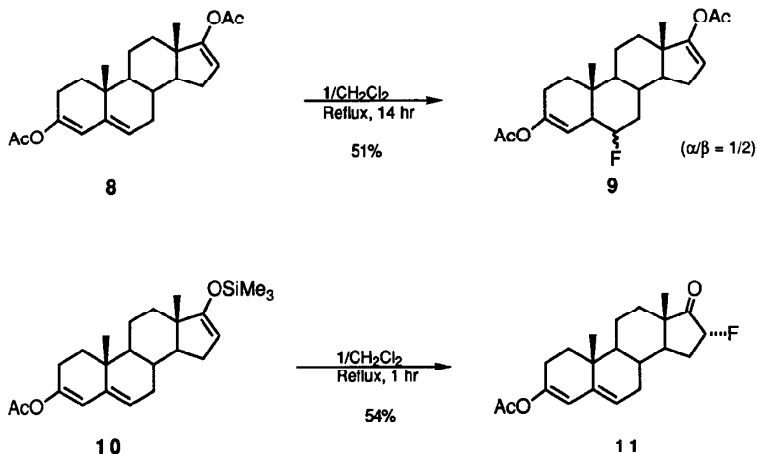
The reactivity of the N-fluoropyridinium salts can be adjusted by varying the substituents on the pyridine ring. Triflates **1-4**, whose fluorinating power increases in the order **2** < **1** < **3** < **4**, are the most generally useful reagents. The most powerful reagent available is **5**;¹⁵ **6** and **7**¹⁶ recently have been developed as mild, efficient reagents. The reagents are all stable, crystalline materials and thus can be handled routinely. Examples of fluorinations which illustrate their use are given in Table I. The weakest reagent **2** is most suited for fluorinating reactive or easily oxidized compounds, such as carbanions, enamines, and sulfides, whereas the more potent reagents **4** and **5** are preferred for fluorinating aromatic rings. Salt **1** of Intermediate

reactivity is effective with moderately electron-rich substrates, such as enol alkyl ethers, enol silyl ethers, and activated vinyl acetates.



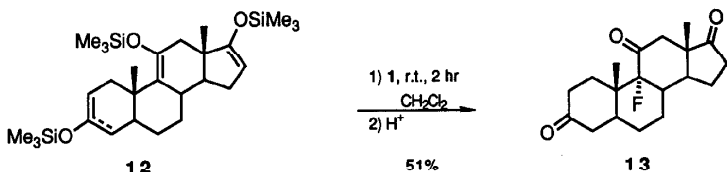
N-Fluoropyridinium triflate shows high regioselectivity in its fluorinations, as evidenced by the results in Schemes 1 and 2. With steroids **8** and **10**, each having two reactive sites, **1** reacts to give exclusively the 6-fluoro steroid **9** and the 16-fluoro steroid **11**, respectively. Thus **1** can distinguish between a conjugated and non-conjugated vinyl acetate, and between an enol silyl ether and a conjugated vinyl acetate in its fluorinations. The present procedure for converting the estrone enol silyl ether to the 16 α -fluoroestrone also shows that **1** selectively reacts with an enol silyl ether moiety in the presence of an activated aromatic ring.

Scheme 1



The fluorination of **12**, easily prepared from the corresponding triketo steroid, with an equimolar amount of **1** (Scheme 2) shows the remarkable ability of **1** to distinguish di-substituted from tri-substituted enol silyl ethers. The 9 α -fluoro steroid **13** is produced in 51% yield (78% based on recovered triketo steroid) and the combined yield of the other fluorinated products is only 4.6%.¹⁷ It thus is apparent that **1** reacts almost exclusively with the trisubstituted enol ether moiety. The new, selective direct fluorination at the 9 α -position holds considerable promise as a means to prepare biologically important 9 α -fluoro steroids.¹⁸

Scheme 2



With the increasing importance of organofluorine compounds in the development of new materials, pharmaceuticals, and agricultural chemicals, N-fluoropyridinium salts should find extensive use as mild and selective fluorinating agents.

1. (a) Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan; (b) Onoda Cement Company, Japan. Present address for T.U.: Daikin Industries, Ltd., Chemical Division, 1-1 Nishi Hitotsuya, Settsu-Shi, Osaka 566, Japan.
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16. Harasawa, K.; Tomita, K.; Umemoto, T., presented at the 52nd Symposium on Organic Synthesis, Tokyo, November 5, 1987.
17. Kawada, K.; Onodera, K.; Umemoto, T., presented at the Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, December 4, 1987.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number) (Registry Number)

N-Fluoropyridinium triflate: Pyridinium, 1-fluoro-, salt with trifluoromethanesulfonic acid (1:1) (12); (107263-95-6)

Pyridine (8,9); (110-86-1)

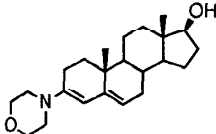
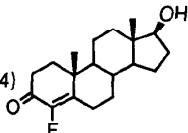
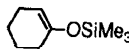

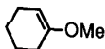
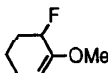

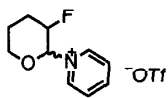
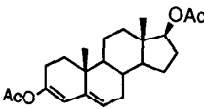
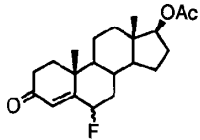
Sodium triflate: Methanesulfonic acid, trifluoro-, sodium salt (8,9); (2926-30-9)

Trifluoromethanesulfonic acid: Methanesulfonic acid, trifluoro- (8,9); (1493-13-6)

Fluorine (8,9); (7782-41-4)

TABLE I

ELECTROPHILIC FLUORINATIONS WITH N-FLUOROPYRIDINIUM TRIFLATES

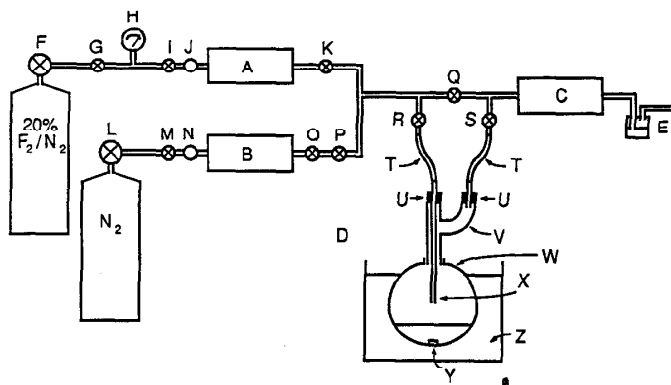
Substrate	Reagent ^a	Conditions	Product	Yield (%) ^b
$n\text{-C}_{12}\text{H}_{25}\text{MgCl}$	2	0°C, 30 min in Et ₂ O	$n\text{-C}_{12}\text{H}_{25}\text{F}$	75 ^c
$\text{NaCH}(\text{COOEt})_2$	2	0°C, 2 hr in THF	$\text{CHF}(\text{COOEt})_2$ $\text{CF}_2(\text{COOEt})_2$	42 6
$\text{CH}_2(\text{COOEt})_2$	2^d	AlCl_3 , ^e 80°C 24 hr in $\text{CH}_2\text{ClCH}_2\text{Cl}$	$\text{CF}_2(\text{COOEt})_2$ $\text{CHF}(\text{COOEt})_2$	76 ^f 19 ^f
$p\text{-ClC}_6\text{H}_4\text{SCH}_3$	2	R.t., 8 hr in CH_2Cl_2	$p\text{-ClC}_6\text{H}_4\text{SCH}_2\text{F}$	76
	2	1) -15°C, 1 hr in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (1/4)		54
	1	2) R.t., ca. 12 hr in c. HCl/DMF		46
	1	R.t., 7 hr in CH_2Cl_2		87 ^c
	1	60°C, 30 min in $\text{CH}_2\text{ClCH}_2\text{Cl}$		63 ^f
	1	Reflux, 7 hr in CH_2Cl_2		86 ^h
	1	Reflux, 10 hr in CH_2Cl_2		71 ⁱ

PhOH	3	Reflux, 5 hr in CH ₂ Cl ₂	F-C ₆ H ₄ OH (o:p)	57 ^c (3.3:1)
PhOMe	3	80°C, 18 hr in CH ₂ ClCH ₂ Cl	F-C ₆ H ₄ OMe (o:p)	64 ^c (1:1)
PhOMe	4	Reflux, 23 hr in CH ₂ Cl ₂	F-C ₆ H ₄ OMe (o:p)	65 ^c (1:1)
PhNHCOOEt	3	80°C, 5 hr in CH ₂ ClCH ₂ Cl	F-C ₆ H ₄ NHCOOEt (o:p)	54 (2.2:1)

a) Equimolar N-fluoropyridinium triflate unless noted otherwise. b) Isolated yields unless noted otherwise. c) GLPC yields. d) 2 Equivalents of **2**. e) 0.4 Equivalents of AlCl₃. f) ¹⁹F NMR yields. g) 1.5 Equivalents of dihydropyran. h) cis/trans = 1/1.

i) $\alpha/\beta = 1/2$.

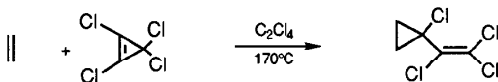
Figure 1



A: Flowmeter (Matheson model 7825); B: Flowmeter (Hastings model CST); C: Alumina trap; D: Reactor system; E: Bubble counter containing perfluorotributylamine; F: Pressure regulator (Matheson model 63-5512); G, I, K, O, P: Stainless steel valves; H: Pressure gauge (Matheson model 63-5512); J, N: Stainless steel filters; L: Pressure regulator for nitrogen; M, Q, R, S: Brass valves; T: Viton tubing; U: Teflon corks; V: Pyrex Claisen adaptor; W: Pyrex flask; X: Pyrex tube; Y: Teflon-coated stirring bar; Z: -40°C Cooling bath.

1-CHLORO-1-(TRICHLOROETHENYL)CYCLOPROPANE

(Cyclopropane, 1-chloro-1-(trichloroethenyl)-)



Submitted by Thomas Liese, Frank Jaekel, and Armin de Meijere.¹

Checked by John R. Berry, James S. Piecara, and Bruce E. Smart.

1. Procedure

A 1-L Hastelloy C-276 shaker tube (Note 1) fitted with a temperature sensor, rupture-disk safety device, and a gas-inlet valve attached to an ethylene cylinder is charged with 120.0 g (0.675 mol) of freshly distilled tetrachlorocyclopropene (Note 2), 350 mL of dry tetrachloroethylene (Note 3), and 10 g of anhydrous sodium carbonate (Note 4). The tube is pressurized to 20 atm with ethylene and shaken for 3 hr. The ethylene cylinder is disconnected, the pressure vessel is gradually heated to 170°C over a 30-min period, and it is shaken at this temperature for 19.5 hr. The vessel is allowed to cool to room temperature, and the excess ethylene is slowly released and bubbled through a wash bottle containing methylene chloride (Note 5). The light brown liquid in the shaker tube is decanted and the remaining solid washed twice with 50 mL of methylene chloride. The organic phases are combined and the methylene chloride is removed by distillation. The residual liquid is distilled at water-aspirator vacuum through a 40-cm Vigreux column. The solvent tetrachloroethylene, bp 35°C (27 mm), is collected (Note 6), followed by 104.1-105.6 g (75-76%) of 1-chloro-1-(trichloroethenyl)cyclopropane as a colorless liquid, bp 81-83°C (27 mm) (Note 7).

2. Notes

1. The submitters used a 1-L autoclave lined with Hastelloy C-4. Hastelloy C materials are high nickel alloys. A highly resistant alloy is employed to avoid possible side reactions.
2. Tetrachlorocyclopropene was prepared from sodium trichloroacetate and trichloroethylene.^{2,3} It is also available from the Aldrich Chemical Company, Inc., Eastman Organic Chemicals, and the Merck-Schuchardt Company (in Europe).
3. Tetrachloroethylene was obtained from the Aldrich Chemical Company, Inc. and distilled from phosphorus pentoxide prior to use.
4. Anhydrous sodium carbonate was obtained from the J. T. Baker Chemical Company and dried under vacuum at 130°C.
5. The wash bottle serves to trap any product carried with the ethylene vapors. to monitor and control the release of ethylene pressure and to indicate when no excess pressure remains, and to diminish the release of toxic materials.
6. The receiver was cooled in an ice bath to avoid loss of the tetrachloroethylene distillate.
7. The submitters obtained 111-116 g of product, bp 72-75°C (14-18 mm). The spectral properties of 1-chloro-1-(trichloroethenyl)cyclopropane are as follows; IR (neat) cm^{-1} : 3100 (CH), 3020 (CH), 1585 (C=C), 1415, 1170, 1040, 1015, 940, 910, 875, 800, 750, 645; ^1H NMR (CDCl_3) δ : 1.42 (m, 2 H), 1.52 (m, 2 H).

3. Discussion

Tetrachlorocyclopropene has been known for some time to be a reasonably reactive dienophile.⁴ Its thermal ring opening to perchlorovinyl carbene is in accord with the behavior of other cyclopropenes under thermolytic conditions,⁵ but the

efficiency with which this vinyl carbene intermolecularly adds to a wide variety of olefins^{6,7} is unprecedented. The resulting 1-chloro-1-(trichloroethenyl)cyclopropanes^{6,7} can be reductively dechlorinated to vinylcyclopropanes,⁶ transformed into variously-substituted cyclopropylacetylenes^{7,8} or cyclopropylidenacetates.⁹ The simple cyclopropyl derivatives, accessible from the reported 1-chloro-1-(trichloroethenyl)cyclopropane, like methyl 2-chloro-2-cyclopropylidenacetate (see accompanying procedure) and 1-trimethylsilyl-1-(trimethylsilylethynyl)cyclopropane (prepared by reductive silylation with magnesium/chlorotrimethylsilane in tetrahydrofuran¹⁰), are especially useful building blocks for the construction of complex organic molecules.^{11,12,13}

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Appendix

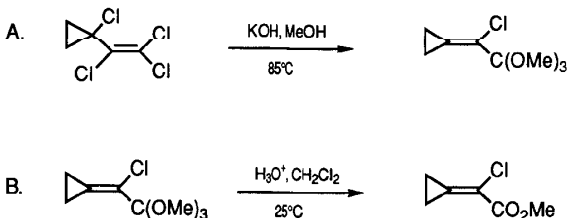
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Chloro-1-(trichloroethenyl)cyclopropane: Cyclopropane, 1-chloro-1-(trichloroethenyl)- (11); (82979-27-9)

Tetrachlorocyclopropene: Cyclopropene, tetrachloro- (8,9); (6262-42-6)

METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE

(Acetic acid, chlorocyclopropylidene-, methyl ester)



Submitted by Thomas Liese, Fereydoun Seyed-Mahdavi, and Armin de Meijere.¹

Checked by James S. Piecara and Bruce E. Smart.

1. Procedure

A. Trimethyl 2-chloro-2-cyclopropylidenethanoate. A 1-L, two-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is charged with 40.0 g (0.19 mol) of 1-chloro-1-(trichloroethenyl)cyclopropane (Note 1), 120 g of potassium hydroxide, and 300 mL of methanol (Note 2). The mixture is stirred for 16-18 hr in an oil bath at 85°C. After the solution is cooled to room temperature, it is diluted with 1 L of ice water. The mixture is then transferred to a 3-L separatory funnel and extracted with three 200-mL portions of ether. The combined ether phases are washed with three 150-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed from the filtrate by distillation at atmospheric pressure, and the residue is distilled through a short-path column under water-aspirator vacuum to give 14.5-15.4 g (39-41%) of trimethyl 2-chloro-2-cyclopropylidenethanoate, bp 103-105°C (20 mm) (Notes 3 and 4).

B. Methyl 2-chloro-2-cyclopropylidenacetate. A 250-mL, one-necked, round-bottomed flask is charged with 60 mL of methylene chloride (Note 2), 3.5 g of a strongly acidic ion-exchange resin (Note 5), and 11.0 g (0.057 mol) of trimethyl 2-chloro-2-cyclopropylidenorthoacetate. The mixture is stirred for 12 hr at room temperature. The ion-exchange resin is removed by filtration and washed with three 10-mL portions of methylene chloride. The combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and distilled at atmospheric pressure to remove the solvent. The residue is distilled through a short-path column under reduced pressure to give 6.2-6.7 g (74-80%) of methyl 2-chloro-2-cyclopropylidenacetate, bp 95-97°C (10 mm) (Notes 6, 7, and 8).

2. Notes

1. 1-Chloro-1-(trichloroethenyl)cyclopropane was prepared from tetrachloro-cyclopentene as described in the accompanying procedure, p. 144.
2. Methanol and methylene chloride were obtained from E. M. Science (Merck & Company, Inc.) and used without further purification.
3. The checkers obtained the same yields for 0.10-mol scale runs. The submitters report yields of 54-58%, however.
4. The submitters report bp 107-109°C (20 mm). The spectral properties of 2-chloro-2-cyclopropylidenorthoacetate are as follows: IR (neat) cm^{-1} : 2840 (OCH_3), 1780 ($\text{C}=\text{C}$); ^1H NMR (CDCl_3) δ : 1.27-1.80 (m, 4 H), 3.23 (s, 9 H).
5. The checkers used analytical grade AG 50W-X8 resin, which is a strongly acidic polystyrene gel type resin, supplied by Bio-Rad Laboratories. The submitters used the large-pore, strongly acidic ion-exchange resin Lewatit SPC 118, supplied by Bayer AG.

6. The submitters report obtaining 7.0-7.5 g (84-90%) of product, bp 60-63°C (3.7 mm), and note that 4.7-5.0 g of analytically pure material, mp 33-34°C, can be obtained by crystallization at -20°C from 10-15 mL of pentane and the remaining 2.3-2.5 g of product can be recovered from the mother liquor by chromatography on silica gel (60 g) using a 5:1 mixture of pentane/diethyl ether as the eluent.

7. The product obtained by the checkers is pure by NMR analysis and it shows the following spectral properties: IR (neat) cm^{-1} : 3080 (cyclopropyl CH), 1720 (C=O); ^1H NMR (CDCl_3) δ : 1.42-1.52 (m, 2 H), 1.69-1.78 (m, 2 H), 3.84 (s, 3 H).

8. The submitters report that the product can be obtained in higher yields without isolation of the intermediate orthoester according to the following procedure: To a solution of sodium methoxide, freshly prepared by dissolving 14.0 g (0.61 mol) of sodium metal in 200 mL of dry methanol, at 65°C is added with stirring 30.0 g of 1-chloro-1-(trichloroethenyl)cyclopropane. The stirred mixture is refluxed (oil bath temperature of 110°C) for 72 hr. After the solution is cooled to room temperature, 200 mL of ice water is added and the mixture is extracted with three 200-mL portions of ether. The combined ether extracts are washed with three 50-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed from the filtrate by distillation at atmospheric pressure. The residue is dissolved in 100 mL of methylene chloride, 10 g of a strongly acidic ion-exchange resin is added (Note 5), and the mixture is stirred at room temperature for 48 hr. The resin is removed by filtration and is washed with three 10-mL portions of methylene chloride. The combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and the solvent is removed from the filtrate by distillation at atmospheric pressure. The residual oil is taken up in 200 mL of pentane and the solution is refrigerated at 5°C. The precipitated crystals are collected by filtration to yield 11-13 g (51-60%) of 2-chloro-2-cyclopropylidenacetate. The checkers obtained a 50% yield of pure product, mp 40-41°C, when this procedure was repeated on about half the scale.

3. Discussion

This procedure is applicable to a number of substituted 1-chloro-1-(trichloroethenyl)cyclopropanes,² and in general gives good yields of methyl 2-chloro-2-cyclopropylidenacetates.³ These are highly reactive Michael acceptors which rapidly react with nucleophiles to give 1'-substituted-2-chloro-2-cyclopropylacetates. The parent 2-chloro-2-cyclopropylidenacetate is a particularly useful building block in organic synthesis since it adds to cyclic dienolates to give complex skeletons in high yields.^{4,5} In addition, it is a reactive dienophile^{5,6} and can be further modified to 2-arylthio-substituted derivatives as well as to the parent methyl 2-cyclopropylidenacetate in high yields.⁷ The corresponding ethyl 2-cyclopropylidenacetate has been prepared in poor yield by a Wittig-Horner-Emmons olefination of cyclopropanone hemiacetal magnesium salt (8%),⁸ and more recently in vastly improved yield (87%) by the benzoic acid-catalyzed Wittig olefination.⁹

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Appendix

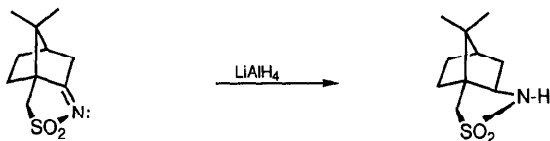
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 2-chloro-2-cyclopropylidenacetate: Acetic acid, chlorocyclopropylidene methyl ester (11); (82979-45-1)

Trimethyl 2-chloro-2-cyclopropylidenorthoacetate: Cyclopropane, (1-chloro-2,2,2-trimethoxyethylidene)- (11); (82979-34-8)

1-Chloro-1-(trichloroethenyl)cyclopropane: Cyclopropane, 1-chloro-1-(trichloroethenyl)- (11); (82979-27-9)

SYNTHESIS OF (-)-D-2,10-CAMPHORSULTAM
(3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-
8,8-dimethyl-2,2-dioxide, (3aS)-)



Submitted by Michael C. Weismiller, James C. Towson, and Franklin A. Davis.¹

Checked by David I. Magee and Robert K. Boeckman, Jr.

1. Procedure

(-)-2,10-Camphorsultam. A dry, 2-L, three-necked, round-bottomed flask is equipped with a 1.5-in egg-shaped Teflon stirring bar, a 250-mL addition funnel, and a 300-mL Soxhlet extraction apparatus equipped with a mineral oil bubbler connected to an inert gas source. The flask is charged with 600 mL of dry tetrahydrofuran (THF) (Note 1) and 6.2 g (0.16 mol) of lithium aluminum hydride (Note 2). Into the 50-mL Soxhlet extraction thimble is placed 35.0 g (0.16 mol) of (-)-(camphorsulfonyl)imine (Note 3) and the reaction mixture is stirred and heated at reflux. After all of the (camphorsulfonyl)imine has been siphoned into the reaction flask (3-4 hr), the mixture is allowed to cool to room temperature. The unreacted lithium aluminum hydride is cautiously hydrolyzed by dropwise addition of 200 mL of 1 N hydrochloric acid via the addition funnel (Note 4). After the hydrolysis is complete the contents of the flask are transferred to a 1-L separatory funnel, the lower, silver-colored aqueous layer is separated, and the upper layer placed in a 1-L Erlenmeyer flask. The aqueous phase

is returned to the separatory funnel and washed with methylene chloride (3 x 100 mL). After the reaction flask is rinsed with methylene chloride (50 mL), the organic washings are combined with the THF phase and dried over anhydrous magnesium sulfate for 10-15 min. Filtration through a 300-mL sintered glass funnel of coarse porosity into a 1-L round-bottomed flask followed by removal of the solvent on a rotary evaporator gives 33.5 g (95%) of the crude (-)-2,10-camphorsultam. The crude sultam is placed in a 250-mL Erlenmeyer flask and crystallized from approximately 60 mL of absolute ethanol. The product is collected on a 150-mL sintered glass funnel of coarse porosity and dried in a vacuum desiccator to give 31.1 g (88%) of the pure sultam. A second crop of crystals can be gained by evaporating approximately half the filtrate; the residue is crystallized as above to give 1.4 g (4%). The combined yield of white crystalline solid, mp 183-184°C, $[\alpha]_D -30.7^\circ$ (CHCl₃, c 2.3) is 92% (Notes 5, 6).

2. Notes

1. Tetrahydrofuran (Aldrich Chemical Company, Inc.) was distilled from sodium benzophenone.
2. Lithium aluminum hydride was purchased from Aldrich Chemical Company, Inc.
3. (-)-(Camphorsulfonyl)imine, [(7S)-(-)-10,10-dimethyl-5-thia-4-azatricyclo-[5.2.1.0^{3,7}]dec-3-ene 5,5-dioxide] was prepared by the procedure of Towson, Weismiller, Lal, Sheppard, and Davis, *Organic Syntheses*, 1990, 69, 158.
4. The addition must be very slow at first (1 drop/5 sec) until the vigorous reaction has subsided.

5. The NMR spectrum of (-)-2,10-camphorsultam is as follows: ^1H NMR (CDCl_3) δ : 0.94 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.33 (m, 1 H), 1.47 (m, 1 H), 1.80-2.05 (5 H), 3.09 (d, 1 H, $J = 14$), 3.14 (d, 1 H, $J = 14$), 3.43 (m, 1 H), 4.05 (br s, 1 H, NH); ^{13}C NMR (CDCl_3) δ : 20.17 (q, CH_3), 26.51 (t), 31.55 (t), 35.72 (t), 44.44 (d), 47.15 (s), 50.08 (t), 54.46 (s), 62.48 (d).

6. Checkers obtained material having the same mp ($183\text{--}184^\circ\text{C}$) and $[\alpha]_D -31.8^\circ$ (CHCl_3 , c 2.3).

3. Discussion

(-)-2,10-Camphorsultam was first prepared by the catalytic hydrogenation of (-)- (camphorsulfonyl)imine over Raney nickel.² Lithium aluminum hydride reduction was used by Oppolzer and co-workers in their synthesis of the sultam.^{3,4} However, because of the low solubility of the sultam in tetrahydrofuran, a large amount of solvent was required.⁴ In the procedure described here the amount of solvent is significantly reduced by using a Soxhlet extractor to convey the imine slowly into the reducing medium.⁵

Oppolzer's chiral auxiliary,⁶ (-)-2,10-camphorsultam, is useful in the asymmetric Diels-Alder reaction,^{3,4} and for the preparation of enantiomerically pure β -substituted carboxylic acids⁷ and diols,⁸ in the stereoselective synthesis of Δ^2 -isoxazolines,⁹ and in the preparation of N-fluoro (-)-2,10-camphorsultam, an enantioselective fluorinating reagent.¹⁰

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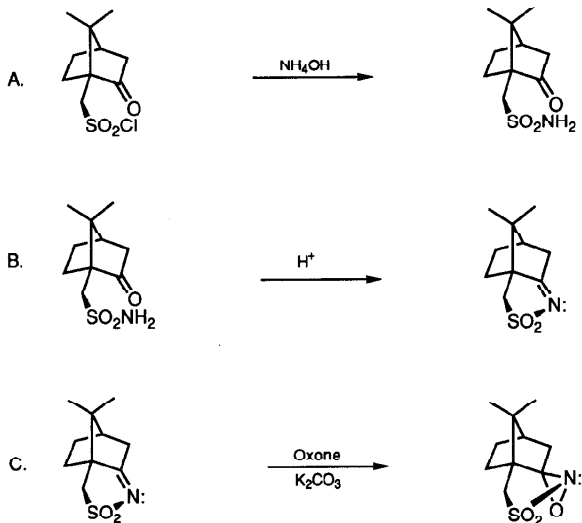
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (-)-(Camphorsulfonyl)imine: 3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-, 2,2-dioxide, (3aS)- (9); (60886-80-8)
- (-)-D-2,10-Camphorsultam: 3H-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-, 2,2-dioxide, [3aS-(3a α ,6 α ,7a β)]- (11); (94594-90-8)

SYNTHESIS OF (+)-(2R,8aS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE
(4H-4a,7-Methanooxazirino[3,2-l][2,1]benziso-thiazole,
tetrahydro-9,9-dimethyl-, 3,3-dioxide, [4aS-(4a α ,7 α ,8aR⁺)])



Submitted by James C. Towson, Michael C. Weismiller, G. Sankar Lal,
 Aurelia C. Sheppard, and Franklin A. Davis.¹

Checked by David I. Magee and Robert K. Boeckman, Jr.

1. Procedure

A. *(+)-(1S)-10-Camphorsulfonamide.* Into a 2-L, three-necked, round-bottomed flask equipped with mechanical stirrer, 65-mm Teflon stirring blade, and a 250-mL

dropping funnel is placed 450 mL of reagent grade ammonium hydroxide. The reaction mixture is cooled to 0°C in an ice bath and stirred vigorously. A solution of 50.0 g (0.2 mol) of (+)-10-camphorsulfonyl chloride (Note 1) in 450 mL of methylene chloride is then added dropwise in two portions over 30 min. The reaction mixture is stirred for an additional 2 hr at this temperature, transferred to a 1000-mL separatory funnel and the phases are separated. The aqueous phase is washed with methylene chloride (2 x 100 mL) and the combined organic extracts are dried for 10-15 min over anhydrous magnesium sulfate. Filtration and removal of the solvent using a rotary evaporator gives 41.5 g (90%), mp 125-128°C, of the crude sulfonamide (Notes 2 and 3).

B. (-)-(Camphorsulfonyl)imine. A 1-L, round-bottomed flask is equipped with a two-inch egg-shaped magnetic stirring bar, a Dean-Stark water separator, and a double-walled condenser containing a mineral oil bubbler connected to an inert gas source. Into the flask are placed 5 g of Amberlyst 15 ion exchange resin (Note 4) and 41.5 g of the crude (+)-(1S)-camphorsulfonamide in 500 mL of toluene. The reaction mixture is heated at reflux for 4 hr. After the reaction flask is cooled, but while it is still warm (40-50°C), 200 mL of methylene chloride is slowly added to dissolve any (camphorsulfonyl)imine that crystallizes. The solution is filtered through a 150-mL sintered glass funnel of coarse porosity and the reaction flask and filter funnel are washed with an additional 75 mL of methylene chloride.

Isolation of the (-)-(camphorsulfonyl)imine is accomplished by removal of the toluene on the rotary evaporator. The resulting solid is recrystallized from absolute ethanol (750 mL) to give white crystals, 34.5-36.4 g (90-95%), mp 225-228°C; $[\alpha]_D^{25}$ -32.7° (CHCl₃, c 1.9) (Note 5).

C. (+)-(2R,8aS)-10-(Camphorylsulfonyl)oxaziridine. A 5-L, three-necked, round-bottomed Morton flask is equipped with an efficient mechanical stirrer, a 125-mm Teflon stirring blade, a Safe Lab stirring bearing (Note 6), and a 500-mL addition

funnel. Into the flask are placed the toluene solution of (-)-(camphorsulfonyl)imine (39.9 g, 0.187 mol) prepared in Step B and a room temperature solution of 543 g (3.93 mol, 7 equiv based on oxone) of anhydrous potassium carbonate dissolved in 750 mL of water. The reaction mixture is stirred vigorously and a solution of 345 g (0.56 mol, 6 equiv of KHSO₅) of oxone dissolved in 1250 mL of water is added dropwise in three portions over 45 min (Notes 7 and 8). Completion of the oxidation is determined by TLC (Note 9) and the reaction mixture is filtered through a 150-mL sintered glass funnel of coarse porosity to remove solids. The filtrate is transferred to a 3-L separatory funnel, the toluene phase is separated and the aqueous phase is washed with methylene chloride (3 x 100 mL). The filtered solids and any solids remaining in the Morton flask are washed with an additional 200 mL of methylene chloride. The organic extracts are combined and washed with 100 mL of saturated sodium sulfite, dried over anhydrous magnesium sulfate for 15-20 min, filtered and concentrated on the rotary evaporator. The resulting white solid is crystallized from approximately 500 mL of hot 2-propanol to afford, after drying under vacuum in a desiccator, 35.9 g (84%) of white needles, mp 165-167°C, [α]_D +44.6° (CHCl₃, c 2.2) (Notes 10, 11).

(-)-(2S,8aR)-10-(Camphorylsulfonyl)oxaziridine is prepared in a similar manner starting from (-)-10-camphorsulfonyl chloride; mp 166-167°C, [α]_D -43.6° (CHCl₃, c 2.2).

2. Notes

1. (-)-10-Camphorsulfonyl chloride was prepared from 50 g of (1S)-(+)-10-camphorsulfonic acid purchased from Aldrich Chemical Company, Inc. using the procedure described by Bartlett and Knox, *Org. Synth., Coll., Vol. V* **1973**, 196. Material that was collected on the suction filter and air dried by maintaining suction for 15-20 min was of sufficient purity for the next step. The checkers obtained comparable

or better overall yields of sulfonamide (96%) without isolation of the acid chloride based on (+)-camphoric acid using thionyl chloride to convert the acid to the acid chloride.

2. The crude sulfonamide is contaminated with 5-10% of the (camphorsulfonyl)imine the yield of which increases on standing.

3. The ^1H NMR spectrum of (+)-(1S)-10-camphorsulfonamide is as follows: (CDCl_3) δ : 0.93 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40-2.50 (m, 7 H), 3.14 and 3.53 (ab quartet, 2 H, $\text{CH}_2\text{-SO}_2$, $J = 15.1$), 5.54 (br s, 2 H, NH_2).

4. Amberlyst 15 ion-exchange resin is a strongly acidic, macroreticular resin purchased from Aldrich Chemical Company, Inc.

5. The spectral properties of (-)-(camphorsulfonyl)imine are as follows: ^1H NMR (CDCl_3) δ : 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45-2.18 (m, 6 H), 2.65 (m, 1 H), 3.10 and 3.28 (AB quartet, 2 H, $\text{CH}_2\text{-SO}_2$, $J = 14.0$); ^{13}C NMR (CDCl_3) δ : 19.01 (q, CH_3), 19.45 (q, CH_3), 26.64 (t), 28.44 (t), 35.92 (t), 44.64 (d), 48.00 (s), 49.46 (t), 64.52 (s), 195.52 (s); IR (CHCl_3) cm^{-1} : 3030, 2967, 1366. Checkers obtained material having identical melting point and $[\alpha]_D -32.3^\circ$ (CHCl_3 , c 1.8).

6. The SafeLab Teflon bearing can be purchased from Aldrich Chemical Company, Inc. A glass stirring bearing lubricated with silicone grease is unsatisfactory because the dissolved salts solidify in the shaft causing freezing.

7. Efficient stirring is important and indicated by a milky white appearance of the solution.

8. Occasionally batches of oxone purchased from Aldrich Chemical Company, Inc., have exhibited reduced reactivity in this oxidation. Oxone exposed to moisture prior to use also gives reduced reactivity in this oxidation. If this occurs oxone is added until oxidation is complete as determined by TLC (Note 9). Potassium carbonate is added as needed to maintain the pH at approximately 9.0. Oxone stored

in the refrigerator under an inert atmosphere has shown no loss in reactivity for up to six months.

9. Oxidation is generally complete after addition of the oxone solution. The oxidation is monitored by TLC as follows: remove approximately 0.5 mL of the toluene solution from the nonstirring solution, spot a 250-micron TLC silica gel plate, elute with methylene chloride and develop with 10% molybdophosphoric acid in ethanol and heating: (camphorsulfonyl)imine $R_f = 0.28$ and (camphorylsulfonyl)oxaziridine $R_f = 0.62$. If (camphorsulfonyl)imine is detected, stirring is continued at room temperature until the reaction is complete (See Note 8).

If the reaction mixture takes on a brownish color after addition of oxone and has not gone to completion after 30 min, the reaction mixture is filtered through a 150-mL sintered glass funnel of coarse porosity, and the solids are washed with 50 mL of methylene chloride. The aqueous/organic extracts are returned to the 5-L Morton flask, stirred vigorously and 52 g (0.08 mol, 1 equiv KHSO_5) of oxone is added over 5 min and stirring continued until oxidation is complete (approximately 10-15 min).

10. The submitters employed a toluene solution of crude imine prepared in part B and obtained somewhat higher yields (90-95%). However, the checkers obtained yields in this range on one half the scale using isolated sulfonylimine.

11. The spectral properties of (+)-(camphorsulfonyl)oxaziridine are as follows: ^1H NMR (CDCl_3) δ : 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45-2.18 (m, 6 H), 2.65 (d, 1 H), 3.10 and 3.28 (AB quartet, 2 H, $\text{CH}_2\text{-SO}_2$, $J = 14.0$); ^{13}C NMR (CDCl_3) δ : 19.45 (q, CH_3), 20.42 (q, CH_3), 26.55 (t), 28.39 (t), 33.64 (t), 45.78 (d), 48.16 (s), 48.32 (t), 54.07 (s), 98.76 (s). The checkers obtained material (mp 165-167°C) having $[\alpha]_D^{25} +44.7^\circ$ (CHCl_3 , c 2.2).

3. Discussion

(Camphorsulfonyl)imine has been reported as a by-product of reactions involving the camphorsulfonamide.²⁻⁵ Reychler in 1898 isolated two isomeric camphorsulfonamides,² one of which was shown to be the (camphorsulfonyl)imine by Armstrong and Lowry in 1902.³ Vandewalle, Van der Eycken, Oppolzer and Vulloud described the preparation of (camphorsulfonyl)imine in 74% overall yield from 0.42 mol of the camphorsulfonyl chloride.⁶ The advantage of the procedure described here is that, by using ammonium hydroxide, the camphorsulfonyl chloride is converted to the sulfonamide in >95% yield.⁷ The sulfonamide is of sufficient purity that it can be used directly in the cyclization step, which, under acidic conditions is quantitative in less than 4 hr. These modifications result in production of the (camphorsulfonyl)imine in 86% overall yield from the sulfonyl chloride.

In addition to the synthesis of enantiomerically pure (camphorylsulfonyl)oxaziridine⁷ and its derivatives,⁸ the (camphorsulfonyl)imine has been used in the preparation of (-)-2,10-camphorsultam (Oppolzers' auxiliary),^{6,9} (+)-(3-oxocamphorylsulfonyl)oxaziridine¹⁰ and the N-fluoro-2,10-camphorsultam, an enantioselective fluorinating reagent.¹¹

The N-sulfonyloxaziridines are an important class of selective, aprotic oxidizing reagents.¹² Enantiomerically pure N-sulfonyloxaziridines have been used in the asymmetric oxidation of sulfides to sulfoxides (30-91% ee),¹³ selenides to selenoxides (8-9% ee),¹⁴ disulfides to thiosulfonates (2-13% ee),⁵ and in the asymmetric epoxidation of alkenes (19-65% ee).^{15,16} Oxidation of optically active sulfonimines ($R^*SO_2N=CHAr$) affords mixtures of N-sulfonyloxaziridine diastereoisomers requiring separation by crystallization and/or chromatography.¹³


(+)-(Camphorylsulfonyl)oxaziridine described here is prepared in four steps from inexpensive (1S)-(+)- or (1R)-(+)-10-camphorsulfonic acid in 77% overall yield.⁷

Separation of the oxaziridine diastereoisomers is not required because oxidation is sterically blocked from the exo face of the C-N double bond in the (camphorsulfonyl)imine. In general (camphorsulfonyl)oxaziridine exhibits reduced reactivity compared to other N-sulfonyloxaziridines. For example, while sulfides are asymmetrically oxidized to sulfoxides (3-77% ee) this oxaziridine does not react with amines or alkenes.⁷ However, this oxaziridine is the reagent of choice for the hydroxylation of lithium and Grignard reagents to give alcohols and phenols because yields are good to excellent and side reactions are minimized.¹⁷ This reagent has also been used for the stereoselective oxidation of vinylolithiums to enolates.¹⁸

The most important synthetic application of the (camphorylsulfonyl)oxaziridines is the asymmetric oxidation of enolates to optically active α -hydroxy carbonyl compounds.^{12c,19-22} Chiral, nonracemic α -hydroxy carbonyl compounds have been used extensively in asymmetric synthesis, for example, as chiral synthons, chiral auxiliaries, and chiral ligands. This structural array is also featured in many biologically active natural products. This oxidizing reagent gives uniformly high chemical yields regardless of the counterion and stereoselectivities are good to excellent (50-95% ee).¹⁹⁻²² Since the configuration of the oxaziridine three-membered ring controls the stereochemistry, both α -hydroxy carbonyl optical isomers are readily available. Representative examples of the asymmetric oxidation of prochiral enolates by (+)-(2R,8aS)-camphorylsulfonyl)oxaziridine are given in Tables I and II.

TABLE I

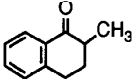
ASYMMETRIC OXIDATION OF LITHIUM ENOLATES OF ESTERS AND AMIDES
USING (+)-(2R,8aS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

Entry	RC(R')=C(OLi)X			Cosolvent	Temp. (°C)	Product		
	R	R'	X			%Yield ^a	%ee (Config.)	Ref.
1	Ph	H	OCMe ₃	----	-90	82	71 (R)	19
2	PhCH ₂	H	OMe	----	-90	73	58 (R)	19
				HMPA	-90	63	85 (R)	
3	Ph	Me	OMe	----	-78	61	45 (R)	19
4	Ph	H	NC ₄ H ₈	----	-78	70	30 (S)	19
				HMPA	-78	74	50 (R)	
5	Ph	Me	NC ₄ H ₈	----	-78	40	35 (S)	19
				HMPA	-78	35	20 (R)	
								
6	Ph	Me		----	-78	53	48 (S)	21
7				HMPA	-78	65	89 (S)	

^aIsolated yields.

TABLE II

ASYMMETRIC OXIDATION OF KETONE-DERIVED ENOLATES USING (+)-(2R,8aS)-
10-(CAMPHORYLSULFONYL)OXAZIRIDINE

Entry	Ketone	Base/ Cosolvent	Temp. (°C)	α -Hydroxy Ketone		
				%Yield ^a	%ee (Config.)	Ref.
1	PhC(O)CH ₂ Ph	LDA	0	70	68 (S)	20
2		LDA/HMPA	0	64	6 (S)	
3		NHMDS ^b	-78	84	95 (S)	
4	PhC(O)CH ₂ Me	LDA	0	51	43 (S)	20
5		NHMDS	-78	73	62 (S)	
6	Me ₃ CC(O)CH ₂ Me	LDA	0	55	32 (R)	23
7		NHMDS	-78	71	89 (R)	
8	PhCH ₂ C(O)Me	NHMDS	-78	70	40 (S)	23
9		NHMDS/HMPA	-78	76	76 (R)	23
10		LDA	0	75	30 (R)	23
11		NHMDS	0	80	16 (R)	23

^aIsolated yields. ^bBis(trimethylsilyl)amide.

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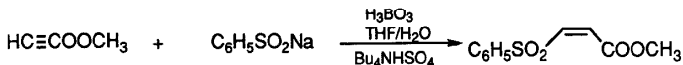
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (+)-(2R,8aS)-10-(Camphorylsulfonyl)oxaziridine: 4H-4a,7-Methanooxazirino-[3,2-i][2,1]benzisothiazole, tetrahydro-9,9-dimethyl-3,3-dioxide, [4aS-(4a α ,7 α ,8aR*)]- (11); (104322-63-6)
- (+)-(1S)-10-Camphorsulfonamide: Bicyclo[2.2.1]heptane-1-methanesulfonamide, 7,7-dimethyl-2-oxo- (1S)- (9); (60933-63-3)
- (+)-10-Camphorsulfonyl chloride: Bicyclo[2.2.1]heptane-1-methanesulfonyl chloride, 7,7-dimethyl-2-oxo-, (+)- (9); (21286-54-4)
- (1S)-(+)-10-Camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1S)- (9); (3144-16-9)
- (-)-(Camphorsulfonyl)imine: 3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-, 2,2-dioxide, (3aS)- (9); (60886-80-8)
- Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate (9); (37222-66-5)

METHYL (Z)-3-(BENZENESULFONYL)PROP-2-ENOATE
(2-Propenoic acid, 3-(phenylsulfonyl)-, methyl ester, (Z)-)



Submitted by G. C. Hirst¹ and P. J. Parsons.

Checked by Annette Prella and Ekkehard Winterfeldt.

1. Procedure

Caution! Methyl propiolate is a lachrymator and must be handled in a fume hood.

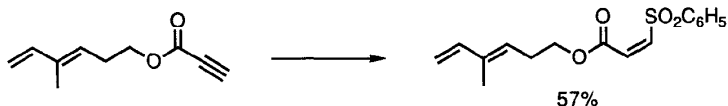
A two-phase mixture of methyl propiolate (5.0 g, 59.5 mmol), boric acid (5.5 g, 89 mmol), sodium benzenesulfinate (9.75 g, 59.5 mmol), and tetra-n-butylammonium hydrogen sulfate (3.0 g, 8.75 mmol) (Note 1) in tetrahydrofuran:water (200 mL, 1:1) is stirred vigorously at room temperature for 48 hr (Note 2). The solution is acidified to pH 4 (2 N hydrochloric acid) and extracted into diethyl ether (4 x 50 mL) (Note 3). The organic layer is dried (MgSO₄) and concentrated under reduced pressure to afford 13.75 g of yellow oil (Note 4) which is subjected to flash column chromatography (1.5:1 hexanes-diethyl ether) to afford initially methyl (E)-3-(benzenesulfonyl)prop-2-enoate (400 mg, 2.9%) and then the desired Z-isomer (10.89 g, 81%) as a pale yellow solid, pure by spectral study (Note 5).

2. Notes

1. All reagents were purchased from Aldrich Chemical Company, Inc. and were used without further purification.
2. A magnetic stirrer is usually adequate. An overhead stirrer was used for the larger scale reported here.
3. Slightly increased yields are observed if most of the organic material is removed under reduced pressure prior to extraction into ether.
4. Purity determines the structure of the product; the crude product is often a yellow solid at this point.
5. The isolated yield has ranged between 71 and 88%. The product has the following spectral and physical characteristics: mp 50.5–51.5°C (ether); IR (CH_2Cl_2) cm^{-1} : 3040 (m), 1732 (s), 1630 (m), 1440 (s), 1340 (s), 1310 (s), 1145 (s); ^1H NMR (CDCl_3 , 360 MHz) δ : 3.92 (s, 3 H, CO_2CH_3), 6.52 (d, 1 H, $J = 11.5$), 6.57 (d, 1 H, $J = 11.5$), 7.55–8.05 (m, 5 H, Ar); ^{13}C NMR (CDCl_3 , 90.56 MHz) δ : 52.43 (q), 127.93 (d), 129.23 (d), 131.5 (d), 133.95 (d), 135.50 (d), 139.42 (s), 164.22 (s); m/z : Found M^+ 226.02890, $\text{C}_{10}\text{H}_{10}\text{O}_4\text{S}$ requires M^+ , 226.02998; 226 (M^+ , 5), 195 (16), 161 (10), 131 (12), 77 (80), 51 (100).

3. Discussion

This procedure describes the short, one-pot, high-yield preparation of methyl (Z)-3-(benzenesulfonyl)prop-2-enoate. This route is shorter than a previously reported preparation.² We have been able to apply this technique to the preparation of a highly functionalized sulfonyl acrylate, although the generality of this reaction has not been studied (eq. 1).³



(1)

Vinyl sulfones in general serve as excellent dienophiles in Diels-Alder reactions,⁴ and we⁵ and others^{2,4} have found the resultant cyclohexene to contain very useful functionality for further manipulation. Hence the vinyl sulfone moiety can serve as a synthon for ethylene,⁶ terminal olefins,⁷ acetylene,⁸ and vinylsilanes⁹ in [4+2]-cycloadditions as well as valuable synthetic intermediates in general.¹⁰

1. Present address: Department of Chemistry, University of California, Irvine, CA 92717. This work was carried out at the University of Southampton, Southampton, U.K. Support from the SERC is gratefully acknowledged.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl (Z)-3-(benzenesulfonyl)prop-2-enoate: 2-Propenoic acid, 3-(phenylsulfonyl) methyl ester, (Z)- (11); (91077-67-7)

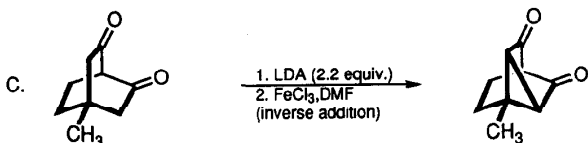
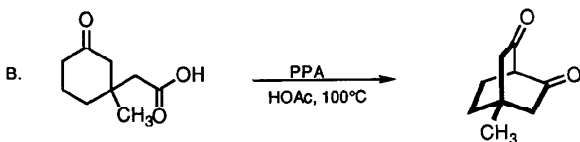
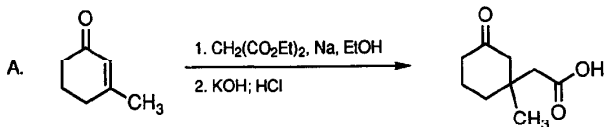
Methyl propiolate: Propiolic acid, methyl ester (8); 2-Propynoic acid, methyl ester (9) (922-67-8)

Sodium benzenesulfinate: Benzenesulfinic acid, sodium salt (8,9); (873-55-2)

INTRAMOLECULAR OXIDATIVE COUPLING OF A BIENOLATE:

4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE

(Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl-)



Submitted by Marc-André Poupart, Gilbert Lassalle, and Leo A. Paquette.¹

Checked by L. A. Stolz and Robert K. Boeckman, Jr.

1. Procedure

A. *3-Methylcyclohexanone-3-acetic acid*. A 2-L, three-necked Morton flask fitted with a low-temperature thermometer, 250-mL addition funnel, an exit tube attached to a calcium chloride drying tube, and a Teflon-coated magnetic stirring bar, is charged with 1.1 L of anhydrous ethanol. The stirred solution is cooled to 0°C and

23 g (1 mol) of sodium cut into small pieces is added through the exit tube. During the addition, the temperature of the reaction mixture increases; therefore, cooling is applied (Note 1). After all of the sodium has completely reacted, 160.2 g (1 mol) of neat diethyl malonate is slowly added through the addition funnel while the temperature is maintained at 0°C (Note 2). At this point, 110.2 g (1 mol) of 3-methyl-2-cyclohexen-1-one (Note 3) is gradually introduced through the addition funnel at 0°C. A white precipitate eventually appears. After 9 days of stirring, the brown reaction mixture is poured onto ice, brought to neutrality with concentrated hydrochloric acid while being vigorously stirred, and extracted with one 600-mL portion and four 300-mL portions of ether (Note 4). The combined organic layers are washed with three 250-mL portions of saturated brine and dried over anhydrous magnesium sulfate. After evaporation under reduced pressure to remove the solvent, the residual oil is distilled through a 20-cm Vigreux column under reduced pressure. The first fraction (bp <60°C at 0.15 mm) consists of a mixture of unreacted starting materials. The second fraction (bp 145-165°C at 1.5 mm), a mixture of diesters (Note 5), is a colorless oil: 202-205 g (74-76%).

In a 2-L, one-necked, round-bottomed flask fitted with a magnetic stirring bar is placed 99 g (0.366 mol) of the diesters. A 1.0-M solution of potassium hydroxide (750 mL, 0.75 mol) is added to the flask with stirring. The mixture is stirred overnight and subsequently heated to reflux for 1 hr. After the mixture is cooled, it is acidified with 100 mL of concd hydrochloric acid and gently boiled for 20 min. Following return to room temperature, the mixture is transferred to a 2-L separatory funnel and extracted with dichloromethane (6 x 100 mL). The combined organic layers are washed with saturated brine (100 mL) and dried over sodium sulfate. The solvent is removed in a rotary evaporator and the residue is distilled in a Kugelrohr apparatus (140-160°C and 0.3-0.5 mm) to provide 49.3 g (79%) of the keto acid (Note 6).

B. 4-Methylbicyclo[2.2.2]octane-2,6-dione. A 2-L, three-necked, Morton flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser, is charged with 245.0 g of polyphosphoric acid (PPA, Note 7), 26.8 g (158 mmol) of the keto acid, and 427 mL of glacial acetic acid. The vigorously stirred mixture is heated at 100°C for 7 hr. After being cooled, the reaction mixture is diluted with 500 mL of saturated brine and extracted with four 200-mL portions of benzene (Note 8). The combined organic layers are washed with saturated sodium bicarbonate (4 x 100 mL) and brine (1 x 100 mL) solutions, and dried over anhydrous magnesium sulfate. After removal of the solvents on a rotary evaporator, the viscous residue is distilled under reduced pressure in a Kugelrohr apparatus, affording 11.0-13.3 g (46-55%) of cyclized diketone as a colorless liquid, bp 100°C at 0.1 mm, which on standing at room temperature may solidify (Note 9).

C. 4-Methyltricyclo[2.2.2.0^{3,5}]octane-3,5-dione. A 500-mL, one-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar and a rubber septum is charged under nitrogen with a solution of 30.8 mL (220 mmol) of dry diisopropylamine in 170 mL of anhydrous tetrahydrofuran. The solution is cooled to 0°C (acetone-dry ice bath) and 137.5 mL (220 mmol) of a 1.6 M solution of n-butyllithium in hexanes is introduced over a 35-min period. The resulting colorless solution is stirred for 15 min at 0°C and then cooled to -78°C.

The diketone (15.20 g, 100 mmol) is dissolved in 27 mL of dry tetrahydrofuran in a 50-mL, round-bottomed flask and added dropwise through a 16-gauge cannula (nitrogen pressure) during 35 min to the lithium diisopropylamide solution. This mixture is stirred for 30 min at -78°C and is added in turn to 280.4 mL (300 mmol) of a 1.07 M solution of anhydrous ferric chloride (Note 10) in dry dimethylformamide diluted with 39 mL of dry dimethylformamide and contained in a 1-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and cooled to -78°C (Note 11). This addition is accomplished as rapidly as possible through an 8-gauge cannula

(nitrogen pressure). After the reaction mixture is stirred for 2 hr at -78°C , it is quenched by the dropwise addition of 24 mL of dry methanol and allowed to reach room temperature. Saturated brine (300 mL) is added and the entire mixture is filtered through Celite. The aqueous phase is extracted with four 250-mL portions of ether. The combined organic layers are washed with saturated brine (3 x 150 mL) and dried over anhydrous magnesium sulfate. After solvent evaporation under reduced pressure, the residue is chromatographed (100 g of TLC grade silica gel; eluant is 15% ethyl acetate in petroleum ether). There is isolated 6.4-6.5 g (43%, Note 12) of the cyclized diketone as a colorless oil (Note 13) and 1.11 g (7.3%) of starting material.

2. Notes

1. Cooling should be applied to moderate the reaction while maintaining a vigorous evolution of gas or the reaction time is prolonged unduly.
2. Cooling below 0°C will induce precipitation of the sodium diethyl malonate.
3. 3-Methyl-2-cyclohexen-1-one can be purchased from the Aldrich Chemical Company, Inc. or prepared according to a known procedure.² Checkers obtained material from Aldrich Chemical Company, Inc. and Lancaster Synthesis, Inc.
4. The checkers employed 600 mL of ether in the first extraction to ensure separation of the phases.
5. According to the literature,³ these esters consist of the product of Michael addition to 3-methylcyclohexenone and of an isomer arising from rearrangement of this primary adduct.
6. The keto acid exhibits the following spectral properties: IR (neat) cm^{-1} : 3500-2500, 1730, 1705; ^1H NMR (300 MHz, CDCl_3) δ : 1.07 (s, 3 H), 1.61-1.77 (m, 2 H), 1.77-1.97 (m, 3 H), 2.14-2.44 (m, 5 H), 8.4-10 (br s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 21.8, 25.3, 35.7, 38.0, 40.7, 45.4, 53.0, 176.9, 179.7.

7. Polyphosphoric acid can be prepared by the addition of 200 g of phosphorus pentoxide (P_2O_5) to 100 mL of an 85% solution of phosphoric acid and heating to 170°C with vigorous stirring until all of the P_2O_5 is dissolved (ca. 6 hr).

8. Continuous extraction of the aqueous phase with toluene can also be applied for 3 days in order to yield 80% of the diketone after Kugelrohr distillation.

9. The pure diketone is a colorless solid, mp 75-76°C; IR (neat) cm^{-1} : 1735, 1710; 1H NMR (300 MHz, $CDCl_3$) δ : 1.17 (s, 3 H), 1.67-1.73 (m, 2 H), 2.07-2.13 (m, 2 H), 2.22 (ABq, 4 H, $J_{AB} = 8.0$, $\Delta\nu_{AB} = 35.05$), 3.16 (t, 1 H, $J = 2.9$); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 22.7, 25.7, 31.0, 33.9, 50.4, 63.4, 206.6.

10. The 1.07 M anhydrous ferric chloride solution in dimethylformamide is prepared as follows: 178.43 g (1.1 mmol) of anhydrous solid ferric chloride is refluxed over 360 mL of thionyl chloride for 4 days at atmospheric pressure. After the solution is cooled, thionyl chloride is removed by distillation at 20 mm and trapped in a 1-L, round-bottomed flask cooled to -78°C. The solid residue is stirred for 1 hr at room temperature under reduced pressure (ca. 20 mm) and heated at 40°C for 1 hr under high vacuum (ca. 1 mm). Drying without heating is then continued overnight under high vacuum. The flask is filled with argon and cooled to 0°C. Approximately 600 mL of freshly distilled dimethylformamide is then slowly added (exothermic reaction). The entire dissolution of solid ferric chloride is achieved in an ultrasound bath during 24 hr. After decantation, the dark brown solution is transferred under argon to a 1-L volumetric flask and the required level is adjusted with freshly distilled dimethylformamide.

11. The checkers found that vigorous mechanical stirring was required because of the viscosity of the dimethylformamide solution at -78°C; otherwise, diminished yields were observed.

12. The yields obtained range from 40 to 54% depending principally on the rate of the inverse addition and the scale of the reaction.

13. The tricyclic diketone, a colorless oil which slowly solidifies, exhibits mp 34.5-35.0°C; IR (neat) cm^{-1} : 1760, 1710; ^1H NMR (300 MHz, CDCl_3) δ : 1.26 (s, 3 H), 2.00-2.06 (m, 2 H), 2.27-2.30 (m, 2 H), 2.46-2.68 (m, 1 H), 2.68 (d, 2 H, $J = 1.3$); ^{13}C NMR (75 MHz, CDCl_3) δ : 23.3, 26.6, 30.9, 47.1, 48.9, 52.6, 203.5.

3. Discussion

The initial Michael addition step is a modified and improved version of a procedure originally developed by Farmer and Ross.³ The second step involving acid-catalyzed dehydration of the cyclohexanone-3-acetic acid is adapted from earlier work developed for the desmethyl series.⁵

The intermolecular dimerization of ketone enolates to give 1,4-diketones has been accomplished earlier with cupric^{6,7} and ferric salts.⁸ These transition metal salts have also been used to achieve intramolecular carbon-carbon bond formation.^{7,9,10} However, step C represents the only reported example¹¹ of cyclopropane construction via technology of this type.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Methyltricyclo[2.2.2.0^{3,5}]octane-2,6-dione: Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl- (12); (119986-99-1)

3-Methylcyclohexanone-3-acetic acid: Cyclohexaneacetic acid, 1-methyl-3-oxo-. (±)- (12); (119986-97-9)

Diethyl malonate; Malonic acid, diethyl ester (8); Propanedioic acid, diethyl ester (9); (105-53-3)

3-Methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-methyl- (8,9); (1193-18-6)

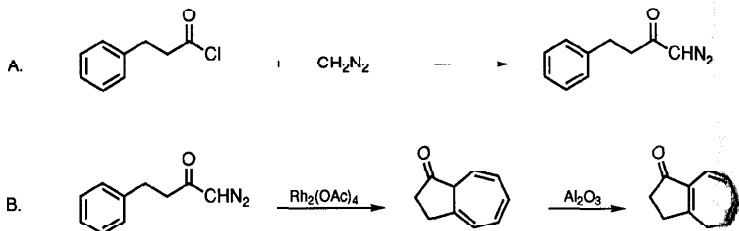
4-Methylbicyclo[2.2.2]octane-2,6-dione: Bicyclo[2.2.2]octane-2,6-dione, 4 methyl- (12); (119986-98-0)

Polyphosphoric acid (8,9); (8017-16-1)

DIAZO KETONE CYCLIZATION ONTO A BENZENE RING:

3,4-DIHYDRO-1(2H)-AZULENONE

(1(2H)-Azulenone, 3,4-dihydro-)



Submitted by Lawrence T. Scott and Chris A. Sumpter.¹

Checked by John M. Fevig and Larry E. Overman.

1. Procedure

Caution! Diazomethane is toxic and explosive; all operations should be carried out in a well-ventilated hood with adequate shielding (Note 1).

A. *1-Diazo-4-phenyl-2-butanone.* A 1-L Erlenmeyer flask equipped with a two-inch magnetic stirring bar and a two-hole rubber stopper fitted with a 125-mL Teflon stopcock separatory funnel (Note 2) and a drying tube filled with potassium hydroxide (Note 3) is charged with a solution of 200 mmol (3.4 equiv) of diazomethane (Note 4) in 600 mL of dry ether. The solution is cooled to 0°C and stirred at high speed (Note 5). To this cooled solution, 10.0 g (59 mmol) of hydrocinnamoyl chloride (3-phenylpropionyl chloride) (Note 6) diluted to 125 mL with anhydrous ether is added dropwise over a 1-hr period. The resulting reaction mixture is stirred cold for an additional 0.5 hr and then at room temperature for 1 hr. After this period of time the

reaction is complete, and excess diazomethane is removed by evacuating the Erlenmeyer flask with a water aspirator pump in the hood (Note 7). The Erlenmeyer flask is evacuated by connecting the aspirator to a one-hole stopper that has been fitted with a plastic or fire-polished glass tube. After the diazomethane has been removed, the remaining ethereal solution is concentrated by rotary evaporation to give 10.5-10.6 g (> 100% crude yield) of 1-diazo-4-phenyl-2-butanone as a yellow oil (Note 8). This oil is used without purification for the next reaction.

B. 3,4-Dihydro-1(2H)-azulenone. A 250-mL, one-necked round-bottomed flask is equipped with an egg-shaped magnetic stirring bar and a high dilution trident (Figure 1)⁴ (Note 9). The high dilution trident is further equipped with a 100-mL pressure-equalizing addition funnel attached to a nitrogen inlet and an efficient reflux condenser attached to a nitrogen outlet. The round-bottomed flask is charged with 100 mL of dry freshly distilled methylene chloride and 12 mg of rhodium diacetate dimer (Note 10). This heterogeneous mixture is stirred at high speed (Note 11) and heated to a rapid reflux without bumping. The addition funnel is charged with a solution of 8.7 g (50 mmol) of 1-diazo-4-phenyl-2-butanone (Note 12) diluted to 50 mL with methylene chloride. As soon as the high dilution trident reservoir (20 mL) fills up and begins to overflow back into the round-bottomed flask, dropwise addition of the diazo ketone solution is initiated (1:20, one drop of diazo ketone solution to every 20 drops of solvent entering the trident reservoir from the condenser). After the addition is complete (2.5-3 hr), the reaction mixture is allowed to reflux for an additional 1 hr. The reaction mixture is then cooled, and the yellow-green solution of the initially-formed unstable trienone (Note 13) is suction-filtered through 110 g of neutral alumina (Note 14) in a 250-mL fritted glass funnel to isomerize the β,γ -double bond into conjugation with the carbonyl group and to remove the rhodium diacetate dimer. The alumina is then washed with 100 mL of ethyl acetate, and the combined organic filtrates are concentrated by rotary evaporation to give a yellow oil. Vacuum distillation of this oil

through a short path distillation head gives 5.5-5.7 g (75-78% yield) of a colorless to slightly green oil that solidifies at 0°C, bp 73-75°C/0.2 mm (Note 15). This material is sufficiently pure for most purposes (Note 16). Recrystallization from hexane (80 mL per gram of trienone) yields colorless needles, mp 28.5-29.0°C (Note 17).

2. Notes

1. See full warning in *Org. Synth., Coll. Vol. II* **1943**, 165, and *Aldrichimica Acta* **1983**, 16(1), 3-10.

2. Ground glass can cause explosions; therefore, a Teflon stopcock must be used.

3. Potassium hydroxide must be used as the drying agent since calcium sulfate and other drying agents can react with diazomethane and cause an explosion.

4. Diazomethane is prepared as described in *Org. Synth., Coll. Vol. IV* **1963**, 250, with 50 g of Diazald (from Aldrich Chemical Company, Inc.) in 300 mL of ether added to 15 g of KOH in 25 mL of water, 30 mL of ether, and 50 mL of 2-(2-ethoxy-ethoxy)ethanol. One equivalent of diazomethane becomes incorporated in the reaction product, and the remainder serves as a scavenger for the HCl produced as a reaction by-product. The excess of diazomethane called for in this procedure is necessary to inhibit the undesired formation of 1-chloro-4-phenyl-2-butanone. The submitters report that this reaction can be performed on twice this scale with comparable results.

5. The high rate of stirring reduces the production of 1-chloro-4-phenyl-2-butanone, a by-product of this reaction.

6. This compound can be purchased from Aldrich Chemical Company, Inc. or prepared according to standard methods.²

7. Two hundred milliliters of ether and diazomethane are removed before transfer for rotary evaporation. Diazomethane in a rotary evaporator can cause explosions.

8. A pure sample of diazo ketone can be obtained by chromatography on silica gel using 15% ethyl acetate/hexane as an eluent, $R_f = 0.37$. The checkers estimate the purity of the crude diazo ketone to be 90-91% based on careful column chromatography of 1.0-g aliquots. They further estimate that approximately 5-6% of 1-chloro-4-phenyl-2-butanone is also produced in the reaction. The spectral properties of 1-diazo-4-phenyl-2-butanone are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 2.59-2.64 (m, 2 H), 2.95 (t, 2 H, $J = 7$) 5.20 (broad s, 1 H), 7.17-7.31 (m, 5 H).

9. The high dilution trident in this example dilutes the diazo ketone solution to 10^{-3} - 10^{-4} M before it reaches the reaction mixture.

10. The rhodium diacetate dimer is used in catalytic amounts; 0.132% (weight of dimer/weight of diazo ketone) has worked out to be the best ratio for this reaction.

11. The high speed stirring minimizes undesired bimolecular reactions.

12. The submitters report that this step can be performed on a 0.5-mol scale (87 g of diazo ketone) in 86.5-94.9% yield. This amount of diazo ketone was prepared in multiple batches as described in Step A. The submitters were reluctant to prepare and handle diazomethane on a scale large enough to make 0.5 mol of diazo ketone in one batch.

13. The initially-formed trienone isomerizes quantitatively to β -tetralone on treatment with catalytic amounts of trifluoroacetic acid. This acid sensitivity precludes chromatography of the crude product on normal silica gel.

14. F20 alumina (60-200 mesh) from Schoofs, Inc. was used. The checkers used chromatography grade neutral alumina (100-125 mesh) supplied by Fluka.

15. The oil bath temperature maximum must be maintained below 120°C or the yield of product drops.

16. The checkers found that on this scale a bulb-to-bulb (Kugelrohr) distillation could also be employed. The distilled product is contaminated with approximately 4-5% of 1-chloro-4-phenyl-2-butanone which was produced in Step A. This impurity is easily removed by recrystallization from hexane. Alternatively, this impurity can be removed at the diazo ketone stage by column chromatography. The use of purified diazo ketone in Step B affords purer distilled product, but this modification has no significant effect on the overall yield.

17. The spectral properties of 3,4-dihydro-1(2H)-azulenone are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 2.50 (narrow m, 2 H), 2.70 (narrow m, 2 H), 2.78 (apparent d, 2 H, $J = 6$), 5.38 (dt, 1 H, $J = 9.6, 6.3$), 6.09 (dd, 1 H, $J = 9.2, 6.2$), 6.47 (dd, 1 H, $J = 11, 5.7$), 6.68 (d, 1 H, $J = 11$); IR (film) cm^{-1} : 1697.

3. Discussion

The cyclopropanation of alkenes, alkynes, and aromatic compounds by carbenoids generated in the metal-catalyzed decomposition of diazo ketones has found widespread use as a method for carbon-carbon bond construction for many years, and intramolecular applications of these reactions have provided a useful cyclization strategy. Historically, copper metal, cuprous chloride, cupric sulfate, and other copper salts were used most commonly as catalysts for such reactions; however, the superior catalytic activity of rhodium(II) acetate dimer has recently become well-established.³ This commercially available rhodium salt exhibits high catalytic activity for the decomposition of diazo ketones even at very low catalyst:substrate ratios (< 1%) and is less capricious than the old copper catalysts. We recommend the use of rhodium(II) acetate dimer in preference to copper catalysts in all diazo ketone decomposition reactions. The present synthesis describes a typical cyclization procedure.

A special feature of the synthesis described here is the glass apparatus used to achieve high-dilution reaction conditions (Figure 1).⁴ This "trident" is simple but effective and can be fabricated quite easily from standard parts. The one shown here is designed to accept an overhead mechanical stirrer.

The product of this synthesis is an especially useful, highly functionalized hydroazulene that is not available commercially. We have used it as a synthetic precursor to homoazulene,⁵ and to a variety of homoazulene derivatives,⁶ bridged homotropylium cations,⁷ and azulene quinones.⁸ It could undoubtedly serve as a precursor to numerous natural products. The cyclization reaction tolerates electron-donating substituents^{3,9} but not halogens¹⁰ on the aromatic ring.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,4-Dihydro-1(2H)-azulenone: 1(2H)-Azulenone, 3,4-dihydro- (9); (52487-41-9)

1-Diazo-4-phenyl-2-butanone: 2-Butanone, 1-diazo-4-phenyl- (8,9); (10290-42-3)

Diazomethane: Methane, diazo- (8,9); (334-88-3)

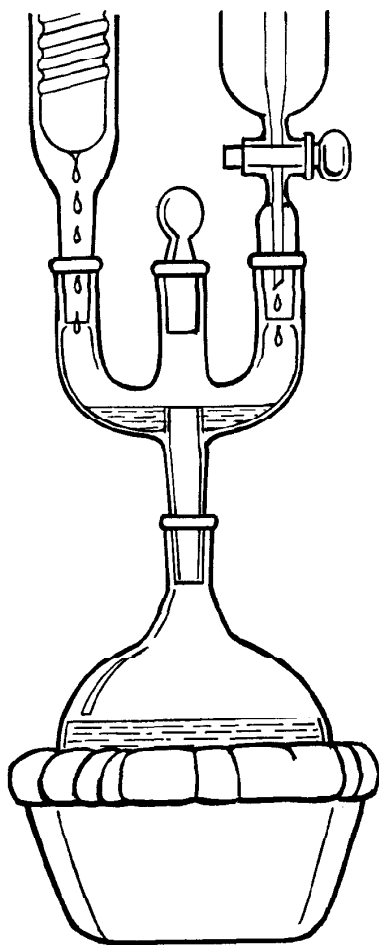
Diazald: p-Toluenesulfonamide, N-methyl-N-nitroso- (8); Benzenesulfonamide, N, 4-dimethyl-N-nitroso- (19); (80-11-5)

2-(2-Ethoxyethoxy)ethanol: Ethanol, 2-(2-ethoxyethoxy) - (8,9); (111-90-0)

Hydrocinnamoyl chloride (8); Benzenepropanoyl chloride (9); (645-45-4)

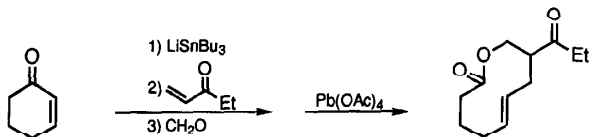
Rhodium diacetate dimer: Acetic acid, rhodium(2+) salt (8,9); (5503-41-3)

Figure 1



**A GENERAL METHOD FOR THE PREPARATION OF 9-, 10-, AND
11-MEMBERED UNSATURATED MACROLIDES: SYNTHESIS OF
8-PROPIONYL-(E)-5-NONENOLIDE**

(2H-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (E)-)



Submitted by Kevin S. Webb, Edward Asirvatham, and Gary H. Posner.¹

Checked by Thais Sielecki and Albert I. Meyers.

1. Procedure

Caution! Benzene has been identified as a carcinogen: OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and gloves should be worn.

A flame-dried (Note 1), 500-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, and an argon inlet is charged with 75 mL of anhydrous tetrahydrofuran (Note 2) and 8.0 mL (57.1 mmol) of diisopropylamine (Note 3), then cooled to -10°C via an ice/salt bath. Next 34.8 mL (55.0 mmol) of butyllithium (1.58 M, Note 4, in hexane) is added dropwise (over 4 min) to the vigorously stirred diisopropylamine solution, and stirred at -10°C for 20 min. Tributyltin hydride (15.2 mL, 55.0 mmol, Note 5) is added dropwise over 5 min to the solution, and the reaction mixture is stirred under argon at -10°C to 0°C for an additional 30 min. The flask is cooled to -78°C and stirred for 20 min.

A flame-dried (Note 1), 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septum, and an argon inlet is charged with 50 mL of anhydrous tetrahydrofuran (Note 2) and 4.85 mL (50.1 mmol) of 2-cyclohexen-1-one (Note 6), and cooled to -78°C . This solution (54.85 mL) is cannulated into the tributyltinlithium solution dropwise over 8 min (Note 7), and the solution is stirred at -78°C under argon for 25 min (Note 8). The same 100-mL, round-bottomed flask is charged with 50 mL of anhydrous tetrahydrofuran (Note 2) and 6.1 mL (59.4 mmol) of ethyl vinyl ketone (Note 9), and cooled to -78°C . This solution (56.1 mL) is cannulated into the 500-mL, round-bottomed flask dropwise over 8 min (Note 10), and the solution is stirred for 1.5 hr (Note 11). The resulting solution is then transferred from a -78°C cold bath to a -23°C cold bath (Note 12) and stirred at this temperature for 30 min.

A flame-dried (Note 1), 100-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, Teflon stopcock, rubber septa, and an argon inlet is charged with 6 g of paraformaldehyde (Note 13). The flask is heated to $165\text{--}170^{\circ}\text{C}$ and the gaseous formaldehyde is bubbled into the -23°C solution (Note 14). After 15 min all of the paraformaldehyde is pyrolyzed (Note 15), and the solution becomes slightly cloudy and yellow. The 500-mL, three-necked, round-bottomed flask is transferred to a -40°C bath (maintained by a Flexicool cryostat) and allowed to stir under argon for 20 hr. The reaction mixture is quenched at -40°C with 7 mL of saturated ammonium chloride followed by 8 mL of distilled water. It is warmed to room temperature, poured into a 500-mL separatory funnel, and diluted with 75 mL of water; the organic layer is separated, and the aqueous layer is extracted with diethyl ether (2 x 100 mL). The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated (Note 16) to afford 29.30 g of crude product.

A flame-dried (Note 1), 1000-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, 24/40 condenser, and an argon inlet is charged with 300 mL of anhydrous benzene (Note 17), and 29.00 g (65.4

mmol) of lead tetraacetate (Note 18). The suspension is heated to 80°C and stirred vigorously under argon. A flame-dried (Note 1), 250-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, and an argon inlet is charged with 150 mL of anhydrous benzene (Note 17) and 29.30 g of the crude reaction mixture. This solution is cannulated into the lead tetraacetate suspension over 2 min (Note 19), and the suspension is allowed to reflux for 2.5 hr. The reaction flask is cooled to room temperature, quenched with 200 mL of distilled water, poured into a 2-L separatory funnel, and diluted with 1000 mL of diethyl ether (Note 20). The organic layer is washed with saturated sodium bicarbonate solution (3 x 200 mL), aqueous 5% hydrochloric acid (2 x 200 mL), distilled water (200 mL) and brine (200 mL). The organic layer is dried over anhydrous magnesium sulfate and filtered; solvent removal afforded 28.95 g of a crude oil. This crude residue (light yellow-brown oil) is purified by short-path column chromatography (Note 21) to yield 4.37 g (41.5%) of 8-propionyl-(E)-5-nonenolide (Notes 22 and 23).

2. Notes

1. All glassware and Teflon-coated magnetic stirring bars were flame-dried under vacuum (0.5 mm) for 5 min, then back-filled with argon. The procedure was repeated a total of three times.

2. Baker reagent grade tetrahydrofuran (99% obtained from Aldrich Chemical Company, Inc.) was distilled over sodium metal spheres/benzophenone under an inert atmosphere and used immediately.

3. Diisopropylamine, 99%, was obtained from Aldrich Chemical Company, Inc., and allowed to reflux over calcium hydride (95+% obtained from Aldrich Chemical Company, Inc.) for 24 hr prior to use.

4. Butyllithium in hexane (1.6 M), obtained from Aldrich Chemical Company, Inc., was titrated (using 2,5-dimethoxybenzyl alcohol as the indicator²) just prior to use.
5. Tributyltin hydride, 97%, was obtained from Aldrich Chemical Company, Inc., and must be used quickly to insure generation of the tributyltinlithium species. Two minutes after the initial addition of tributyltin hydride the colorless solution turned light yellow.
6. 2-Cyclohexen-1-one, 97%, was obtained from Aldrich Chemical Company, Inc., and was freshly distilled via short-path distillation.
7. After the 2-cyclohexenone addition was complete, the 100-mL, round-bottomed flask was washed with 10 mL of anhydrous tetrahydrofuran, and this wash was cannulated into the 500-mL flask (Note 2).
8. A small aliquot of the reaction mixture was removed after 15 min and analyzed by analytical TLC. The TLC was developed in 20% ethyl acetate:hexane and showed that the 1,4-conjugate addition had proceeded to completion ($R_f = 0.58$); the solution was colorless at this point of the reaction.
9. Ethyl vinyl ketone, 97%, was obtained from Aldrich Chemical Company, Inc., and used directly.
10. The reaction mixture turned slightly yellow during addition of ethyl vinyl ketone.
11. A small aliquot was removed from the reaction mixture and analyzed by analytical TLC (20% ethyl acetate:hexane) to insure that the Michael addition had proceeded, $R_f = 0.44$, and $R_f = 0.32$ corresponding to the diastereomeric intermediates.
12. A -23°C bath was obtained from a mixture of dry ice/carbon tetrachloride. A temperature between -40°C and -20°C is necessary.
13. Paraformaldehyde, 95%, was obtained from Aldrich Chemical Company, Inc., and used directly.

14. The argon inlet was equipped with a 16-gauge, 3-inch, syringe needle, the transfer cannula was a flex-needle (Z10,091-9) obtained from Aldrich Chemical Company, Inc., and the outlet bubbler was equipped with a 10-gauge, 3-inch, syringe needle.

15. A high pressure stream of argon was needed to prevent the gaseous formaldehyde from polymerizing to paraformaldehyde in the transfer flex needle.

16. The weight of 29.30 g was achieved by attaching the round-bottomed flask to a vacuum (1.5 mm) and heating via a water bath (55°C) for 4 hr.

17. Benzene (thiophene-free, 99+%, 900 mL) was obtained from Aldrich Chemical Company, Inc., and washed with concentrated sulfuric acid (5 x 100 mL), distilled water (100 mL), aqueous 2% sodium hydroxide solution (100 mL), distilled water (100 mL), and dried over anhydrous magnesium sulfate. It was then allowed to reflux over calcium hydride for 24 hr. The checkers found that the benzene only needed to be distilled from calcium hydride.

18. Lead tetraacetate was purchased from Aldrich Chemical Company, Inc., and used directly.

19. The transfer cannula was a 12-inch, 16-gauge, double-tipped syringe needle, and the 250-mL flask was washed with an additional 30 mL of anhydrous benzene (Note 17), which was cannulated into the 1000-mL flask.

20. The 1000-mL, round-bottomed flask was washed with diethyl ether (3 x 100 mL of the 1000 mL).

21. Working on 1/2 of the present scale, the checkers found that by using Amicon Grace Matrex Silica Gel, (60 Å, 20-45 m) and an eluting solvent of 10% diethyl ether:hexane, 3.50 g (66.0%) of 8-propionyl-(E)-5-nonelide was obtained. The white solid was further purified by recrystallization from 15 mL of hexane to yield 3.15 g (60.0%) as a white solid.

22. The physical properties are as follows: IR (CHCl_3) cm^{-1} : 2933, 1731, 1349, 1210, 1154, 979, 770, 746; ^1H NMR (CDCl_3 , 400 MHz) δ : 1.05 (t, 2 H, $J = 7.2$), 1.12 (t, 1 H, $J = 7.2$), 1.70-3.00 (m, 11 H), 3.76-3.82 (m, 0.67 H), 4.15-4.21 (m, 0.33 H), 5.05-5.70 (m, 3 H). When the proton signals at 1.90-2.90 ppm were irradiated, the two olefinic multiplets collapsed into two doublets ($J = 15.2$). An analytical sample (4.37 g) was recrystallized from 20 mL of hexane (Fisher, certified) to yield 4.05 g (38.5%) as a white solid: mp 70-71°C. Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3$: C, 68.57; H, 8.57. Found: C, 68.47; H, 8.68.

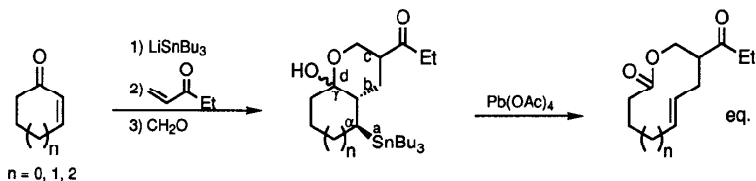
23. In order to determine whether the product was a mixture of geometrical isomers (e.g., differing by cis or trans geometry at the double bond) or conformers it was necessary to obtain ^1H NMR spectra at various temperatures. The 400 MHz ^1H NMR ($\text{DMSO}-d_6$) at 100°C shows that the two triplets (δ 1.05 and 1.12) start to collapse to one triplet, the multiplicity of the peaks in the region of δ 5.05-5.70 simplify greatly, and the initial peak ratios in the region of δ 3.70-4.20 change from 1:2 to 1:3. Therefore, the nonenolide is one pure isomer of only trans double bond geometry and is able to exist as two stable conformers in solution. The glass capillary GC (Hewlett Packard 5890) of 8-propionyl-(E)-5-nonenolide shows only one peak with a retention time of 4.21 min (injector temperature 175°C, detector temperature 225°C).

3. Discussion

The procedure described is a simple, rapid, and convenient method for conversion of n -sized cycloalkanones into $n+4$ alkenolides. Significant but limited progress has been reported in the recent literature toward the preparation of medium and large ring lactones via ring-expansion reactions. One of the most notable and useful developments in this area involves conversion of a cycloalkanone into a bicyclic vinylic ether which is oxidatively cleaved to form a ring-enlarged keto lactone.³

Recently, several variations of this ring-enlargement reaction have been reported including the scission of alkoxy radicals.⁴ In most of these cases, a superfluous functional group (e.g., ketone, iodide) is produced during cleavage of the bicyclic system. Regiospecific conversion of such functional groups into a specific alkene structural unit is usually not possible because of the similar chemical environment α and α' to the functional group.⁵ Because many regiospecifically unsaturated lactones are physiologically active natural products,⁶ we have developed methodology to prepare unsaturated macrolides having a carbon-carbon double bond with specific geometry and at a specific position in the macrolide skeleton.

Because of our interest in one-pot, multicomponent annulations,⁷ we envisioned a flexible and efficient protocol which would link the four different components via the formation of four new bonds (a-d, eq. 1) in one reaction vessel. The intermediate γ -hydroxystannanes thus formed in eq. 1 could be oxidatively fragmented⁸ to produce both ring enlargement and regiospecific formation of an alkenyl unit. This 4-atom ring expansion methodology of common sized α,β -unsaturated ketones has led to the syntheses of many mono- and disubstituted 9-, 10-, and 11-membered unsaturated macrolides (Table).

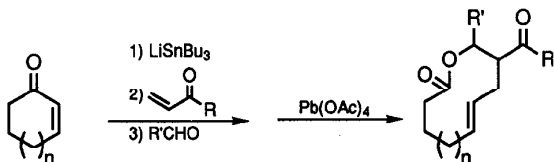


Based on the data in the Table and on our published results,⁷ it is clear that five-, six-, and seven-membered cycloalkenones undergo this 4-atom ring enlargement reaction to produce medium ring, unsaturated lactones in overall yields

of 30-54%. Permutations on this methodology include using either ethyl vinyl ketone or phenyl vinyl ketone as the third component, and either substituted acetaldehydes or substituted benzaldehydes as the last component. The geometrical assignment of the new carbon-carbon double bond was made from interpreting the 400 MHz ^1H NMR decoupled spectra in which each olefinic proton collapsed into a baseline resolved doublet with coupling constants of $J = 15-16$. The proton decoupling experiments conducted to determine the relative stereochemistry of the vicinal substituents in the disubstituted macrolides were inconclusive; often the magnitude of the coupling constants were similar or not discernible from the spectra. Therefore, the relative stereochemistry of the vicinal substituents was established by examining the ^1H NMR spectra of the intermediate γ -hydroxystannanes (usually only two were isolated). The trans-hemiketals showed typical coupling constants of $J = 8-13$, while the cis-hemiketals showed coupling constants of $J = 2-4$. Separate lead tetraacetate oxidative fragmentation of these γ -hydroxystannanes produced two different ring-enlarged lactones both with specific trans-double bond geometry and differing only in the relative stereochemistry of the vicinal substituents.

This homologous Baeyer-Villiger type oxidative ring expansion represents a conceptually new protocol illustrating the substantial value of one-pot, four-component annulations as a flexible and simple new synthetic method.

TABLE



n	R	R'	% Yield	<u>trans:cis</u>
0	Et	CH_3	30.5	0.57
1	Et	CH_3	47	0.7
1	Et	$\text{CH}_2=\text{CH}$	39.5	2.6
1	Et	$o\text{-BrC}_6\text{H}_4$	47	5.3
1	Et	$o\text{-IC}_6\text{H}_4$	37	2.6
1	Ph	$o\text{-IC}_6\text{H}_4$	34	1.0
1	Et	PhCH_2	43.5	1.5
1	Ph	$o\text{-BrC}_6\text{H}_4\text{CH}_2$	30	1.0
1	Et	$o\text{-N(phtl)C}_6\text{H}_4$	42	5.0
1	Et	H	41.5	
1	Et	$2,3\text{-(MeO)}_2\text{C}_6\text{H}_3\text{CH}_2$	52	1.0
1	Ph	$2,3\text{-(MeO)}_2\text{C}_6\text{H}_3\text{CH}_2$	51	1.5
1	Et	3-thienylCH_2	52	0.7
1	Ph	3-thienylCH_2	52	1.8
1	Et	3-furylCH_2	54	0.7
1	Ph	3-furylCH_2	40	7.0
2	Et	Cyclopropyl	53	1.1
2	Et	CH_3	40	1.0
2	Et	$3\text{-(MeO)C}_6\text{H}_4$	41.5	1.5
2	Ph	$o\text{-IC}_6\text{H}_4\text{CH}_2$	38	1.9

1. The Johns Hopkins University, Department of Chemistry, Baltimore, MD 21218.
We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the NSF (CHE 86-07974) for financial support, and Professor S.-S. Jew for experimental help.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

8-Propionyl-(E)-5-nonenolide: 2H-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (E)- (12); (114633-68-0)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (106-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

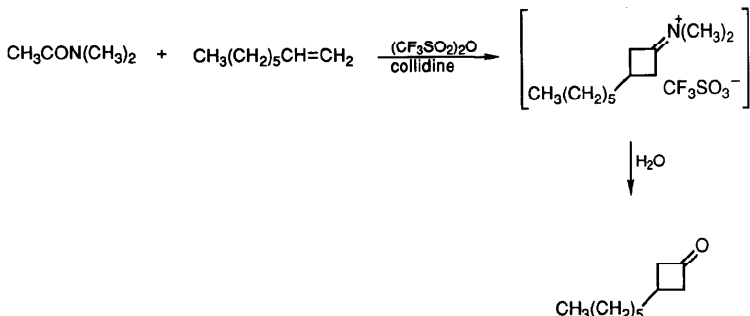
2-Cyclohexen-1-one (8,9); (930-66-7)

Ethyl vinyl ketone: 1-Penten-3-one (8,9); (1629-58-9)

Paraformaldehyde (9); (30525-89-4)

Lead tetraacetate: Acetic acid, lead (4+) salt (8,9); (546-67-8)

**A GENERAL SYNTHESIS OF CYCLOBUTANONES FROM OLEFINS
AND TERTIARY AMIDES: 3-HEXYLCYCLOBUTANONE**



Submitted by C. Schmit, J. B. Falmagne, J. Escudero, H. Vanlierde,
and I. Ghosez.¹

Checked by Thomas J. Sowin and Albert I. Meyers.

1. Procedure

A 500-mL, three-necked flask is equipped with a rubber septum, a magnetic stirring bar, a gas inlet, and a reflux condenser. The top of the condenser is connected to a pressure-equalizing dropping funnel isolated from moisture by a sulfuric acid trap (Note 1). The flask is cooled to -15°C and charged with N,N-dimethylacetamide (3.26 g, 37.5 mmol) (Note 2) in 100 mL of 1,2-dichloroethane (Note 3). The dropping funnel is charged with 1-octene (16.8 g, 150 mmol) (Note 4) and 2,4,6-collidine (5.44 g, 45 mmol) (Note 5) in 50 mL of 1,2-dichloroethane. A slightly positive pressure of argon is maintained in the apparatus throughout the course of the reaction.

Trifluoromethanesulfonic anhydride (12.69 g, 45 mmol) (Note 6) is added through the rubber septum into the solution of N,N-dimethylacetamide by means of a syringe. A precipitate is formed. The olefin-collidine solution is then added dropwise over a period of 20 min. During these operations rapid stirring and cooling are maintained. The resulting mixture is refluxed for 17 hr (Note 7). The solvent is removed by rotary evaporation. The oily residue is washed with dry ether (3 x 20 mL) (Note 8). Then 20 mL of carbon tetrachloride (Note 9) and 20 mL of water are added to the crude cyclobutaniminium salt. The mixture is refluxed for 6 hr (Note 10). The organic phase is separated and the aqueous phase is extracted with carbon tetrachloride (3 x 20 mL). The combined organic phases are dried over anhydrous magnesium sulfate. The solvent is removed by distillation at atmospheric pressure (Note 11). Bulb to bulb distillation (bath temperature 100-110°C, water pump) gives 3.3 g (59%) of 3-hexylcyclobutanone (Notes 12 and 13).

2. Notes

1. The assembled apparatus is flame dried under a slight pressure of argon.
2. N,N-Dimethylacetamide (Janssen Chimica, Beerse, Belgium) is distilled before use. The checkers used it as obtained from Aldrich Chemical Company, Inc.
3. 1,2-Dichloroethane (99%) is obtained from Janssen Chimica or Aldrich Chemical Company, Inc. It is distilled from calcium hydride.
4. 1-Octene (97%) is purchased from Janssen Chimica or Aldrich Chemical Company, Inc. and distilled.
5. 2,4,6-Collidine (99%, Janssen Chimica or Aldrich Chemical Company, Inc.) is distilled from calcium hydride and stored under argon in a brown bottle.

6. Trifluoromethanesulfonic anhydride is prepared just prior to use according to the procedure of Stang, et al.² The checkers obtained it from Aldrich Chemical Company, Inc.

7. During this period the solution turns dark brown and, after rotary evaporation, the residue is a thick, black oil. The progress of the reaction can be followed by IR ($\nu_{C=N^+}$) cm^{-1} : 1730-1735, but the checkers found that it was complete in this 17-hr period.

8. Technical ether is dried over potassium hydroxide.

9. Technical carbon tetrachloride is used. Dichloromethane is preferred only when the cyclobutanone is too volatile.

10. The progress of the hydrolysis can be followed by IR, but the checkers found that it was complete in 6 hr.

11. Rotary evaporation or vacuum distillation can lead to a substantial loss of cyclobutanone.

12. The spectral properties of the compound are as follows: IR (CCl_4 , $\nu_{C=O}$) cm^{-1} 1785; ^1H NMR (270 MHz, CDCl_3) δ : 0.840 (t, 3 H, CH_3), 1.226-1.243-1.302 (m, 8 H, CH_2), 1.513 (m, 2 H, CH), 2.300 (m, 1 H, CH), 2.610 (m, 2 H, CH), 3.079 (m, 2 H, CH); ^{13}C NMR (75.5 MHz, CDCl_3) δ : 13.98, 22.53, 23.78, 28.16, 29.02, 31.71, 36.29, 52.43, 200.61.

13. The physical properties of the semicarbazone are as follows: mp 148.5°C; Anal. Calcd for $\text{C}_{11}\text{H}_{21}\text{N}_3\text{O}$: C, 62.53; H, 10.02; N, 19.88; O, 7.57. Found: C, 62.63; H, 10.05; N, 19.95; O, 7.50.

3. Discussion

Cyclobutanones are important synthetic intermediates. A common synthetic method for their preparation is the [2+2] cycloaddition of olefins with ketenes often

generated in situ from acid chlorides. However, that method suffers limitations especially when aldoketenes and unreactive olefins are used.

Keteniminium salts are more electrophilic than ketenes and are thus able to react with less nucleophilic olefins. Ketoketeniminium salts can be conveniently prepared from the corresponding α -chloro enamines and Lewis acids.³ However, the method cannot be applied well to the preparation of the less stable aldoketeniminium salts.

The method described here which involves the in situ generation of keteniminium triflates is practical and more general. The best results were obtained with 2,4,6-collidine but occasionally the more expensive 2,6-di-*t*-butyl-4-methylpyridine was superior. Pyridine gave satisfactory results in few uses only. Triethylamine always gave poor results. With the more reactive olefins (e.g., styrene), reactions can be run in refluxing dichloromethane. The procedure described here usually gives better yields than that previously reported in a preliminary communication.⁴ It has been used to prepare cyclobutanones as well as cyclobutenones^{5,6} from a wide variety of olefins or acetylenes. A few examples are shown in Table I. The method works well for olefins or acetylenes bearing alkyl, alkenyl or aryl groups. It does not apply to enol ethers or enamines.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

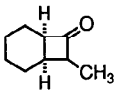
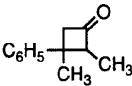
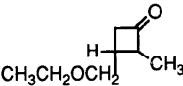
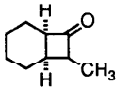
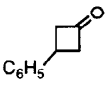

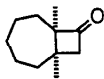
N,N-Dimethylacetamide: Acetamide, N,N-Dimethyl- (8,9); (127-19-5)

1-Octene (8,9); (111-66-0)

2,4,6-Collidine: Pyridine, 2,4,6-trimethyl- (8,9); (108-75-8)

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

TABLE I
SYNTHESIS OF CYCLOBUTANONES FROM TERTIARY AMIDES AND OLEFINS

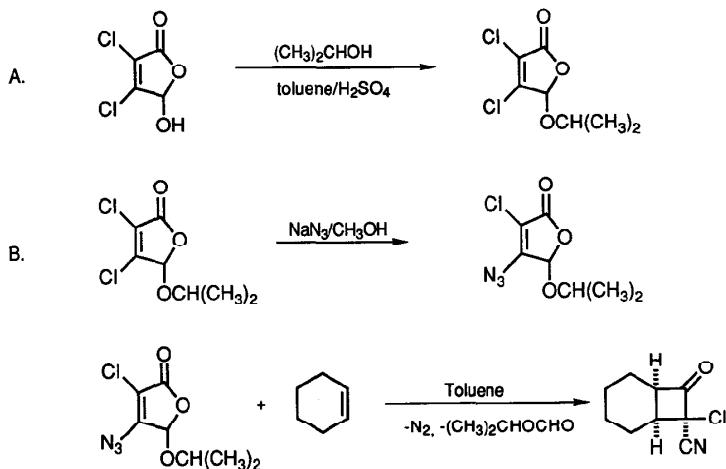
Amide	Olefin	Cyclobutanone	Yield %
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	Cyclohexene		89 ^a
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	α -Methylstyrene		79 ^a
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	Allyl ethyl ether		56 ^a
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Cyclohexene		46
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Styrene		71
$(\text{H}_3\text{C})_2\text{NCO}-\underset{\text{CH}_3}{\text{CH}}(\text{CH}_2)_3\text{CH}=\text{CH}_2$			87 ^b
$(\text{H}_3\text{C})_2\text{NCO}(\text{CH}_2)_6\text{CH}=\text{CH}_2$			71 ^b

^aMixture of endo + exo isomers. ^bThese reactions were performed under slightly different conditions.⁴

7-CHLORO-7-CYANOBICYCLO[4.2.0]OCTAN-8-ONE

(Prepared from Chlorocyanoketene)

(Bicyclo[4.2.0]octane-7-carbonitrile, 7-chloro-8-oxo-, (1 α ,6 α ,7 β)-)



Submitted by Paul L. Fishbein and Harold W. Moore.¹

Checked by Steven Wolff and David L. Coffen.

1. Procedure

A. *3,4-Dichloro-5-isopropoxy-2(5H)-furanone*.² A 1-L, round-bottomed flask equipped with a Dean-Stark trap, condenser, argon bubbler, and magnetic stirrer is charged with 50.7 g (0.30 mol) of mucochloric acid (Note 1), 46 mL (0.60 mol) of isopropyl alcohol, 300 mL of toluene, and 20 drops of concd sulfuric acid. The mixture is heated to reflux with stirring overnight (~18 hr) with separation of water. The

solution is cooled, washed with saturated sodium bicarbonate solution and brine, and dried with magnesium sulfate. After removal of the solvent under reduced pressure, the residue is distilled to give 60.88 g (96%) of the furanone as a clear colorless liquid (bp 90-91°C, 1.5 mm; Lit.² mp 23-24°C, bp 109-111°C, 6 mm).

B. 7-Chloro-7-cyanobicyclo[4.2.0]octan-8-one. To a 250-mL Erlenmeyer flask is added 20.0 g (94.8 mmol) of 3,4-dichloro-5-isopropoxy-2(5H)-furanone and 120 mL of methanol. The flask is cooled in an ice bath with stirring and 7.5 g (115.4 mmol) of sodium azide is added. The ice bath is removed after 15 min and the mixture is stirred for an additional 50 min. After dilution with 600 mL of water, the reaction mixture is extracted with one 100-mL and two 50-mL portions of toluene. The combined organic layers are washed with water (2 x 100 mL) and with 100 mL of brine and are dried with magnesium sulfate. TLC analysis (1:1 ether:hexane, SiO₂) indicates only one component (R_f = 0.38) and no remaining dichlorofuranone (R_f = 0.45) (Note 3).

A 2-L, three-necked flask fitted with a condenser, argon bubbler, thermometer, and addition funnel is charged with 700 mL of toluene (freshly distilled and dried over 4 Å molecular sieves) and 20 mL (Note 4) of cyclohexene (freshly distilled). With magnetic stirring, the mixture is heated to 105°C and the azidofuranone solution prepared above is added over a period of 20 min (Note 5). Upon completion, the reaction mixture is heated for an additional 1.25 hr at 105°C. The solution is cooled and concentrated under reduced pressure to yield a yellow-brown residue which is distilled using a short-path apparatus to give 13.3 g (76%) (bp 85-90°C, 0.5 mm) of the cyclobutanone as a very pale yellow oil which solidifies (mp 34-35°C) upon standing at 4°C (Notes 6 and 7).

2. Notes

1. Practical grade mucochloric acid obtained from Aldrich Chemical Company, Inc. (mp 125-128°C) was used. Unless otherwise stated, all reagents and solvents were of commercial grade. The checkers used mucochloric acid obtained from Eastman Organic Chemicals.

2. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 1795, 1652; ¹H NMR (CDCl₃) δ: 1.31 (d, 6 H, J = 6.2), 4.14 (heptet, 1 H, J = 6.2), 5.87 (s, 1 H); MS (EI): 195 (39), 151 (100), 95 (25); MS (CI): 211 (M⁺+1, 100); Anal. Calcd. for C₇H₈Cl₂O₃: C, 39.84; H, 3.82. Found: C, 39.55; H, 3.84.

3. The submitters isolated and characterized the azidofuranone as a white crystalline solid after recrystallization from petroleum ether (bp 35-60°C), with mp 51.5-52.5°C. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 2130, 1814, 1664; ¹H NMR (CDCl₃) δ: 1.33 (d, 6 H, J = 6.2), 4.17 (heptet, 1 H, J = 6.2), 5.99 (s, 1 H); MS (EI): 217 (M⁺, 6), 158 (34), 119 (28, C₃ClNO + H₂O), 101 (77), 73 (100); MS (CI): 218 (M⁺+1, 55), 120 (10, C₃HClNO + H₂O), 102, (100). Anal. Calcd. for C₇H₈ClN₃O₃: C, 38.64; H, 3.71. Found: C, 38.67; H, 3.65. The azidofuranone decomposes at about 80°C so caution must be exercised when working with it.

4. If an alkene less volatile than toluene is used, 1.1-1.2 equiv of the alkene are satisfactory.

5. The ketene must be generated in situ since it is exceptionally reactive and will undergo self-condensation if permitted.

6. Recrystallization from petroleum ether (35-60°C) in a dry ice/acetone bath afforded colorless crystals with mp 39.5-40.5°C. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 2340, 1838; ¹H NMR (CDCl₃) δ: 1.66 (m, 8 H), 3.03 (m, 1 H), 3.96 (m, 1 H); ¹³C NMR (CDCl₃): 20.72, 21.20, 21.41, 24.25, 36.26, 55.33, 64.17, 115.90, 189.91; MS (EI): 183 (M⁺, 6), 148 (46), 119 (13), 109 (33), 81 (100); MS (CI):

184 (M+1, 84), 156 (100). Anal. Calcd. for $C_9H_{10}ClNO$: C, 58.87; H, 5.49. Found: C, 58.58; H, 5.71.

7 Since chlorocyanocyclobutanones are readily hydrolyzed, protic recrystallization solvents and silica gel chromatography should be avoided. Short path distillation is the method of choice for the purification of most of the cyclobutanones.

3. Discussion

Chlorocyanoketene has been prepared previously by the thermal decomposition of the pseudomethyl ester of the azidofuranone.³ This azide has been used extensively without complication. However, all azides are capable of detonation. The ratio (C+O/N) has been suggested as a threshold value for detonation, which may occur when this ratio is lower than 3:1.⁴ The ratio for the previously used azide is 2.7 while that for the isopropyl analog is 3.3:1.

The synthesis of chlorocyanoketene presented here has advantages over other routes such as dehydrohalogenation of the appropriate acid chloride.⁵ The most obvious advantage is that the ketene is generated slowly during thermolysis. Thus, its concentration is always low. In addition, since it is generated by pyrolytic means, the presence of tert-amines and/or metals is avoided. No other method for the synthesis of chlorocyanoketene has been reported. However, we have found that it can be prepared with difficulty from chlorocyanoacetyl chloride.

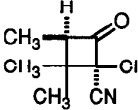
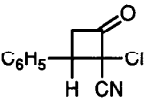
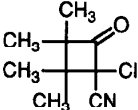
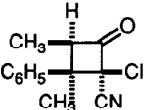
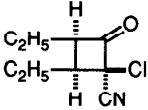
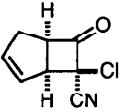
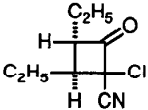
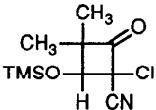
Chlorocyanoacetyl chloride can be made from the extremely hygroscopic acid. It is quite unstable, with 1 g decomposing in 1 hr at room temperature. If a mixture of an imine and triethylamine is treated with the acyl chloride only a dark tar is obtained. However, if the acyl chloride is first treated with the imine, the reaction allowed to subside, and the mixture then treated with triethylamine, the resulting 2-azetidinone is

formed in 63% yield. This is in comparison with the 96% yield obtained by using the azidofuranone.

Other cyclobutanones that can be made with chlorocyanoketene and their respective yields are shown in the Table.

1. Department of Chemistry, University of California, Irvine, CA 92717.
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Table
Other Cyclobutanones From Chlorocyanoketene^{4c}

	80%		86%
	74%		86%
	93%		30%
	67%		70%

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

7-Chloro-7-cyanobicyclo[4.2.0]octan-8-one: Bicyclo[4.2.0]octane-7-carbonitrile,

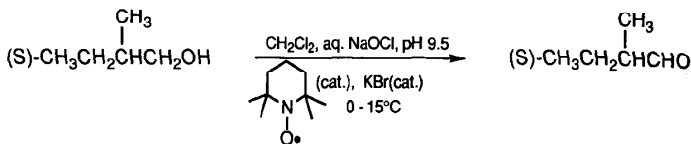
7-chloro-8-oxo-, (1 α ,6 α ,7 β)- (11); (89937-15-5)

3,4-Dichloro-5-isopropoxy-2(5H)-furanone: 2(5H)-Furanone, 3,4-dichloro-5-isopropoxy- (8); 2(5H)-Furanone, 3,4-dichloro-5-(1-methylethoxy)- (9); (29814-12-8)

Mucochloric acid: Malealdehydic acid, dichloro- (8); 2-Butenoic acid, 2,3-dichloro-4-oxo-, (Z)- (9); (87-56-9)

Sodium azide (8,9); (26628-22-8)

**A GENERAL SYNTHETIC METHOD FOR THE OXIDATION OF PRIMARY
ALCOHOLS TO ALDEHYDES: (S)-(+)-2-METHYLBUTANAL**
(Butanal, 2-methyl-, (S)-)



Submitted by Pier Lucio Anelli, Fernando Montanari, and Silvio Quici.¹

Checked by Katsumasa Nonoshita and Hisashi Yamamoto.

1. Procedure

A 1-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer, pressure-equalizing dropping funnel, and a thermometer. The flask is charged with 44.05 g (0.50 mol) of (S)-(+)-2-methyl-1-butanol (Note 1), 0.78 g (5 mmol) of 2,2,6,6-tetramethylpiperidin-1-oxyl (Note 2), 170 mL of dichloromethane, and a solution of 5.95 g (0.050 mol) of potassium bromide in 25 mL of water (Note 3). The reaction mixture is vigorously stirred and cooled to -10°C with a salt-ice bath, then 550 mL (0.55 mol) of 1 M aqueous sodium hypochlorite (Note 4) at pH 9.5 (Note 5) is added over 15-20 min (Note 6), keeping the temperature of the reaction mixture between 10 and 15°C . The mixture is stirred a further 3 min (Note 7). The orange organic phase is separated and the aqueous phase (Note 8) is extracted with 50 mL of dichloromethane. The combined organic extracts are washed with 100 mL of 10% aqueous hydrochloric acid containing 1.6 g (0.010 mol) of potassium iodide (Note 9), 60 mL of 10% aqueous sodium thiosulfate (Note 10) and 60 mL of water (Note 11).

The organic phase is dried over anhydrous magnesium sulfate and then distilled at atmospheric pressure through a 20-cm Vigreux distilling column to give 35.3 - 36.3 g (82-84%) (Note 12) of (S)-(+)-2-methylbutanal as a colorless oil, bp 90-92°C (GC purity > 99%) (Note 13), $[\alpha]_{\text{D}}^{22} +36.8^\circ$ (acetone, c 2.5) (Notes 14, 15, and 16).

2. Notes

1. (S)-(-)-2-Methyl-1-butanol (GC purity > 99.5%; $[\alpha]_{\text{D}}^{20} -6.6 \pm 0.3^\circ$ (ethanol, c 10) was purchased from Fluka Chemie AG. Esterification with (R)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (Mosher's acid)² and subsequent ¹H and ¹⁹F NMR analyses at 300 MHz of the resulting ester showed an enantiomeric purity of (S)-(-)-2-methyl-1-butanol > 99%.

2. 2,2,6,6-Tetramethylpiperidin-1-oxyl from Nacalai Tesque, Inc., Kyoto, Japan, also available from Janssen Chimica, Beerse, Belgium, was used. 4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl, prepared according to the procedure of Endo,³ can also be used.⁴

3. In the absence of potassium bromide longer reaction times are required.⁴

4. Concentrations of aqueous sodium hypochlorite in the range 0.3-2.0 M have been used successfully.

5. The pH (~12.7) of fresh commercial 1 M aqueous sodium hypochlorite is adjusted to 9.5 by dissolving 17 g of sodium hydrogen carbonate per liter immediately before use.

6. If the reaction is carried out on a 1-10 mmol scale, the temperature is easily maintained at 0°C and the reaction is over in a few minutes.⁴ On a larger scale, a very efficient cooling system is required to maintain the temperature at about 0°C. When conventional laboratory equipment is used, the conditions described in this procedure

are a reasonable compromise between two requirements: i) fast addition of the aqueous sodium hypochlorite, and ii) temperature in the reaction medium low enough to minimize the catalyst decomposition.⁴ Longer reaction times increase slightly the formation of 2-methylbutanoic acid.

7. At this stage the reaction can be monitored by GC: 1 m by 3 mm OV 101 5% on Chromosorb HP 100-120 mesh column, 50°C (2 min), then 50°C to 90°C (15°C per min).

8. (S)-(+)-2-Methylbutanoic acid, $[\alpha]_{\text{D}}^{20} +18.7^\circ$ (ethanol, c 1.1) (lit.⁵ $[\alpha]_{\text{D}}^{22} +16.3^\circ$, ethanol, c 1.1) (1.5-2.6 g, 3-5% yield) can be isolated by acidic work up of the aqueous phase.

9. Washing with hydrochloric acid and potassium iodide removes 2,2,6,6-tetramethylpiperidin-1-oxyl from the organic phase.⁶ Because of its volatility, the catalyst cannot be eliminated in the distillation of crude aldehyde.

10. Washing with 10% aqueous sodium thiosulfate leads to a colorless organic phase, indicating total elimination of the catalyst.

11. The aqueous phase must be neutral. Acidic impurities catalyze trimerization of the anhydrous aldehyde⁷ in the distillation stage.

12. Yields can be further increased with a more efficient separation of the (S)-(+)-2-methyl-1-butanol contained in the top fractions.

13. The spectral properties of (S)-(+)-2-methylbutanal are as follows: IR (film) cm^{-1} : 2970, 2940, 2890, 2820, 2710, 1725, 1460; ^1H NMR (300 MHz, CDCl_3) δ : 0.94 (t, 3 H), 1.09 (d, 3 H), 1.33-1.54 (m, 1 H), 1.64-1.85 (m, 1 H), 2.18-2.33 (m, 1 H), 9.63 (d, 1 H).

14. Reduction with borane/tetrahydrofuran⁸ regenerated enantiomerically pure (S)-(-)-2-methyl-1-butanol, as shown by esterification with Mosher's acid and subsequent NMR analysis of the ester (see Note 1).

15. When practical (S)-(-)-2-methyl-1-butanol (GC purity 95%; $[\alpha]_D^{20} -6.3 \pm 0.5^\circ$ (EtOH, c 10) from Fluka Chemie was used, (S)-(+)-2-methylbutanal having $[\alpha]_D^{20} +33.1^\circ$ (acetone, c 2.5) was obtained.

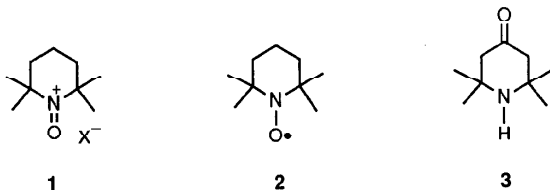
16. Oxidation of (S)-(-)-2-methyl-1-butanol to (S)-(+)-2-methylbutanal has been previously carried out in low yields by chromium oxidation,⁹ under phase transfer catalysis,¹⁰ or by Swern oxidation in the presence of tributylamine.¹¹

3. Discussion

Oxammonium salts **1** have been used extensively either in stoichiometric or in catalytic amounts¹² for the oxidation of primary and secondary alcohols to the corresponding carbonyl derivatives.

The catalytic procedure described here allows a fast, cheap and highly selective conversion of primary alcohols into aldehydes, using sodium hypochlorite as the oxidant in a two-phase (dichloromethane-water) system. Aqueous sodium hypochlorite is buffered at pH 8.6-9.5 to ensure the presence of hypochlorous acid in the organic layer.¹³

Oxammonium salt **1**, the effective oxidant species, is continuously generated from nitroxyl radical **2** by hypochlorous acid in the organic phase. Radical **2** is one of





the most stable radicals known, and is easily prepared from the inexpensive triacetoneamine **3**.¹⁴ The oxidation is very exothermic; for this reason scale up of the reaction needs a very efficient cooling system to maintain the temperature in the optimum 0-15°C range. One one-hundredth (0.01) molar equivalent of nitroxyl radical **2** is generally used, but on this reaction scale the amount of catalyst can be reduced to 0.002 molar equivalent, without substantially affecting the reaction time. Sodium hypochlorite is used in only slight excess and is entirely consumed, an unusual occurrence for reactions carried out under aqueous, organic two-phase conditions.¹⁵

Conversion of saturated, primary alkyl and aryl alkyl alcohols into the corresponding aldehydes can be achieved by this method provided that the alcohols are entirely dissolved in the organic phase. Relatively unstable protective groups are not afforded, as in the oxidation of the acetonide of 1,2,6-hexanetriol, whereas conjugated and isolated double bonds give rise to side reactions which considerably decrease selectivities and yields.⁴ Some examples of aldehydes synthesized with this method are reported in Table 1. Under the same conditions, secondary alcohols are oxidized to ketones. Addition of catalytic amounts of quaternary onium salts allows fast and total conversion of primary alcohols and aldehydes into carboxylic acids making this methodology very versatile.⁴

When the limitations outlined above are considered, the procedure described here appears to be easier and cheaper than most methods in the condensed phase known to date.¹⁶ Furthermore, alkali halides are almost the only contaminants in the waste water, making the scale up of this method very attractive.

TABLE I

OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES

Alcohol	Isolated Yield (%)
1-Heptanol	88
1-Octanol	92
1-Nonanol	92 ⁴
1-Undecanol	93 ⁴
 $(\text{CH}_2)_2\text{-CH}_2\text{OH}^{17}$	85
Benzyl alcohol	90 ⁴
p-Nitrobenzyl alcohol	89
m-Nitrobenzyl alcohol	88
 CH_2OH	75

1. Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy.
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15. (a) Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* **1982**, *101*, 147; (b) Dehmlow, E. V.; Dehmlow, S. S. In "Phase-Transfer Catalysis", 2nd ed.; Ebel, H. F., Ed.; VCH Pubs: New York, 1983.

16. Bomowski, H. In "Methoden der Organischen Chemie" (Houben-Weyl) 4th ed.; Thieme: Stuttgart, 1983; Vol. E/3, pp. 265-300.
17. Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1979**, 134,

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

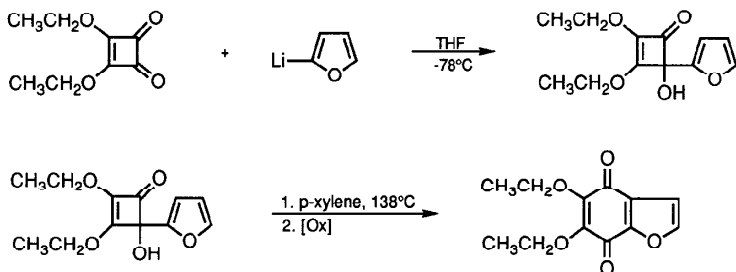
(S)-(+)-2-Methylbutanal: Butyraldehyde, 2-methyl-, (S)-(+)- (8); Butanal, 2-methyl-, (S)-(9); (1730-97-8)

(S)-(-)-2-Methyl-1-butanol: 1-Butanol, 2-methyl-, (S)-(-)- (8); 1-Butanol, 2-methyl-, (S)-(9); (1565-80-6)

Tetramethylpiperidin-1-oxyl: 1-Piperidinyloxy, 2,2,6,6-tetramethyl- (9); (2564-83-2)

4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl: 1-Piperidinyloxy, 4-methoxy-2,2,6,6-tetramethyl (11); (95407-69-5)

REARRANGEMENT OF 4-ARYL-4-HYDROXY-2,3-DIALKOXYCYCLOBUTENEDIONES TO ANNULATED HYDROQUINONES AND QUINONES: 5,6-DIETHOXYBENZOFURAN-4,7-DIONE



Submitted by S. T. Perri, P. Rice, and H. W. Moore.¹

Checked by Ho-Jung Kang and Leo A. Paquette.

1. Procedure

A 500-mL, round-bottomed flask is flame-dried and flushed with nitrogen. The flask is equipped with a magnetic stirring bar and a rubber septum and charged with 4.14 g (60.9 mmol) of furan (Note 1) and 300 mL of dry tetrahydrofuran (Note 2). The solution is stirred and cooled in an ethylene glycol-dry ice bath (-15°C) and 24.17 mL (55.6 mmol) of 2.3 M butyllithium is added slowly by means of a syringe pump (rate = 1.5 mL/min). After complete addition, the solution is stirred an additional 30 min. The ethylene glycol-dry ice bath is replaced with an ice bath and the solution stirred for 1.5 hr at 0°C . The flask is then cooled to -78°C in a dry ice-acetone bath.

A 1000-mL, round-bottomed flask is flame-dried and flushed with nitrogen. The flask is equipped with a magnetic stirring bar and a rubber septum and charged with

9.00 g (52.9 mmol) of diethyl squarate (Note 3) and 450 mL of dry tetrahydrofuran (Note 2). The solution is stirred and cooled in a dry ice-acetone bath at -78°C . The solution of 2-lithiofuran is transferred dropwise via cannula to the flask containing the diethyl squarate which is stirred rapidly. After complete addition (45 min), the solution is stirred for 20 min and quenched by pouring the cold solution into a separatory funnel containing 150 mL of aqueous 10% ammonium chloride and 100 mL of diethyl ether. The separatory funnel is shaken vigorously until phase separation is achieved and all of the ice has melted. The aqueous phase is separated from the organic phase and the aqueous layer is extracted twice with 40-mL portions of diethyl ether. The combined organic layer is washed with 125 mL of brine solution and dried over solid anhydrous potassium carbonate (Note 4) for 5 min with gentle swirling.

The solution is decanted from the potassium carbonate (Note 5) and concentrated on a rotary evaporator (bath temperature = $23\text{--}40^{\circ}\text{C}$) to approximately 150 mL in a 1000-mL round-bottomed flask. Then 400 mL of dry p-xylene (Note 6) is added and the flask is placed on the rotary evaporator at a bath temperature of 40°C to remove the remaining tetrahydrofuran and diethyl ether. The flask containing the remaining p-xylene solution of the cyclobutenone is fitted with a reflux condenser and heated at reflux for 3 hr under nitrogen. The flask is cooled to ambient temperature and the solvent is removed on a rotary evaporator fitted with a bump trap at a bath temperature of 70°C to give a red oil.

The oil is dissolved in 500 mL of diethyl ether and washed with three 200-mL portions of an ethanolic ferric chloride solution (Note 7). The aqueous layers are separated from the organic phase and extracted with four 100-mL portions of diethyl ether. The combined organic layer is washed with saturated sodium bicarbonate solution (Note 8) until the aqueous wash is no longer acidic. The resulting neutralized aqueous extracts are combined and extracted with three 30-mL portions of diethyl ether. The organic extracts are combined, washed with 150 mL of brine solution and

dried over magnesium sulfate. The solution is filtered and concentrated on a rotary evaporator to give the quinone as a red solid. The solid is recrystallized from methanol to yield 10.4-10.5 g of the quinone as orange needles in 2-3 crops (63-64% based on diethyl squarate), mp 54-55°C (Note 9).

2. Notes

1. Furan was purchased from Aldrich Chemical Company, Inc., and used as such.

2. Tetrahydrofuran was distilled under argon from benzophenone ketyl.

3. 3,4-Diethoxy-3-cyclobutene-1,2-dione is commercially available from Aldrich Chemical Company, Inc. *Caution: This substance was found to cause severe skin rashes, and extreme care should be exercised in handling it.* The dimethoxy analog appears to be safer. Diethyl squarate has the following spectral properties: IR (neat) cm^{-1} : 1830, 1741, and 1609; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.47 (t, 6 H, $J = 2.9$), 4.47 (q, 4 H, $J = 7.1$).

4. Prolonged drying of the cyclobutenone over potassium carbonate resulted in product decomposition. Anhydrous magnesium sulfate was found to hydrolyze the product during the thermolysis step.

5. The cyclobutenone was pure enough to use in the next step without purification. This compound is stable for a few hours in solution while kept cold ($<5^\circ\text{C}$) and anhydrous.

6. Certified p-xylene was purchased from Fisher Scientific Company and used as such.

7. Ferric chloride was purchased from Mallinckrodt, Inc. A saturated solution of 80 g of ferric chloride in 500 mL of water was diluted with 500 mL of ethanol, filtered, and used as such. The oxidation could be followed by TLC using Engel stain.

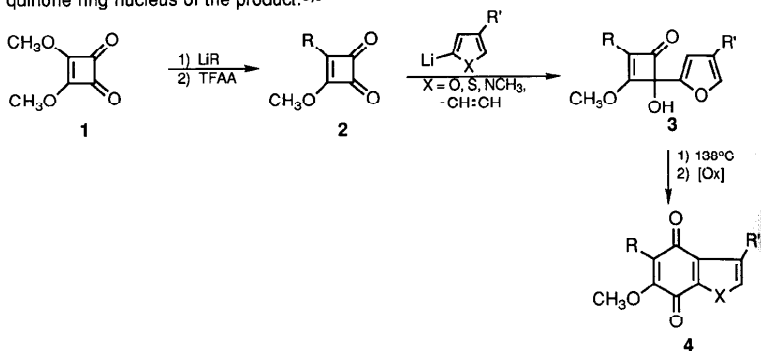
8. Quinones are generally sensitive to bases and some decomposition may occur if the product is exposed for a prolonged period of time to sodium bicarbonate. Therefore the neutralization wash was carried out quickly.

9. The spectral properties of the product are as follows: IR (CHCl_3) cm^{-1} : 2980, 1667, 1480, 1370, 1290, 1250, and 1179; ^1H NMR (CDCl_3 , 500 MHz) δ : 1.42 (2 overlapping t, 6 H, two CH_3), 4.30 (2 overlapping q, 4 H, two CH_2), 6.81 (d, 1 H, $J = 1.9$), 7.67 (d, 1 H, $J = 1.8$); ^{13}C NMR (CDCl_3) δ : 15.7, 15.8, 70.2, 70.3, 108.3, 126.7, 145.7, 146.6, 148.5, 150.1, 172.7, 178.8; EI-MS (70 EV): $m/z = 236$ (19%), 208 (21), 193 (8), 180 (24), 163 (7), 152 (100), 123 (9).

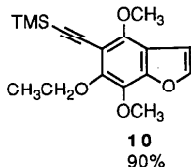
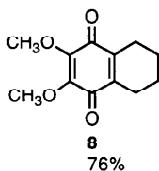
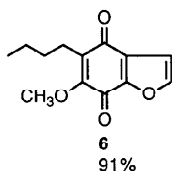
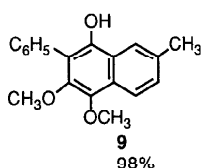
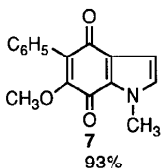
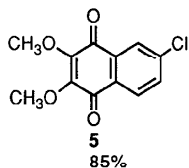
3. Discussion

This procedure describes a synthetic route to annulated hydroquinones/quinones. The example represents a general, convergent, regiospecific and usually high yielding method. This is further elaborated by the generalized scheme given below. Specifically, dialkoxycyclobutenediones, e.g., dimethyl squarate, **1**, are easily converted to unsymmetrical cyclobutenediones **2** upon treatment with an organolithium reagent ($\text{R}=\text{alkyl}$, aryl, alkenyl, alkynyl, -78°C , THF) followed by treatment with trifluoroacetic anhydride (-78°C , TFAA) and an aqueous work-up.^{2,3,4} Treatment of **2** with an aryllithium reagent results in the regiospecific formation of the cyclobutenones **3** via 1,2-addition to the more nucleophilic carbonyl group. These adducts then undergo facile rearrangement to the corresponding annulated hydroquinones in refluxing *p*-xylene. The product is usually isolated as the quinone **4** after an oxidative work-up.^{5,6,7} It is noted that alkenyl lithium reagents as well as alkynyl analogs also add regiospecifically to the cyclobutenediones **2** to give the corresponding cyclobutenones. The alkenyl adducts, like the aryl analogs, also rearrange to the corresponding hydroquinones. The alkynyl

adducts rearrange directly to the corresponding quinones via a unique pathway involving migration of the alcoholic proton of the 4-hydroxycyclobutenone to the quinone ring nucleus of the product.^{8,9}



Compounds **5-10** are specific examples of annulated products which have been prepared by the method outlined here.



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Appendix

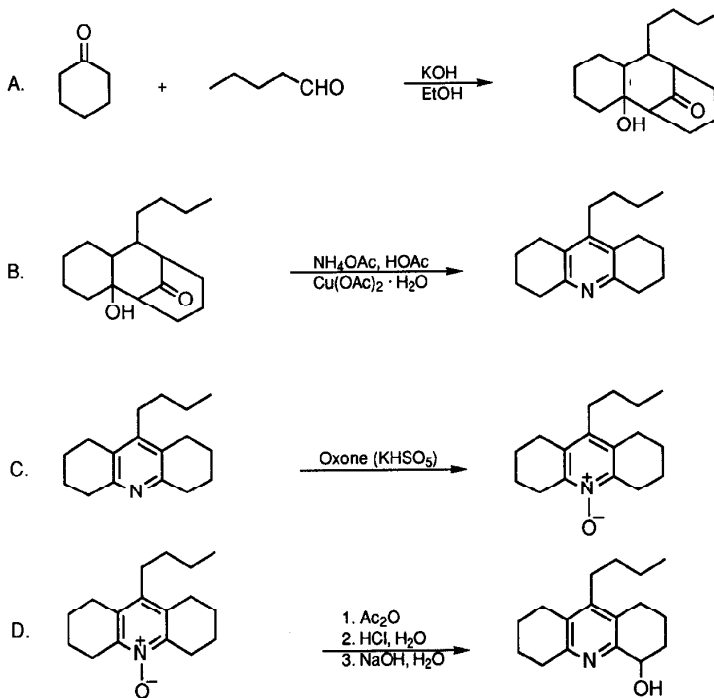
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Furan (8,9); (110-00-9)

Diethyl squarate: Cyclobutenedione, diethoxy- (8); 3-Cyclobutene-1,2-dione, 3,4-diethoxy- (9); (5231-87-8)

9-n-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL

(4-Acridinol; 9-butyl-1,2,3,4,5,6,7,8-octahydro-)



Submitted by Thomas W. Bell, Young-Moon Cho, Albert Firestone, Karin Healy,
Jia Liu, Richard Ludwig and Scott D. Rothenberger.¹

Checked by Edward R. Holler, Jr. and Bruce E. Smart .

1. Procedure

A. 8-*n*-Butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one. A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, 500-mL pressure equalizing dropping funnel, and a reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler. The flask is flushed with nitrogen and then charged with 1.0 L (947 g, 9.65 mol) of cyclohexanone (Note 1). The cyclohexanone is stirred and heated to 70-75°C under nitrogen, a solution of 9.0 g (0.14 mol) of potassium hydroxide (Note 2) in 85 mL of absolute ethanol is added in one portion, and then a solution of 150 mL (122 g, 1.4 mol) of pentanal (Note 3) in 140 mL of absolute ethanol is added dropwise over a period of 8 hr while maintaining the reaction mixture at 70-75°C. The reaction mixture is stirred and held at 70-75°C for an additional 12 hr, and then allowed to cool to room temperature. The reaction flask is immersed in an ice bath, the inner wall of the flask is scratched with a glass rod to initiate crystallization, and the mixture is kept at 0°C for 4 hr to complete the crystallization. The colorless crude product is collected by vacuum filtration and washed with 200 mL of cold ether. The filtrates are combined and concentrated to approximately 200 mL with a rotary evaporator. The precipitated white solid is collected by filtration and washed with water (2 x 200 mL) and 200 mL of cold ether to give a second crop of crude product. The two crops are combined and recrystallized from 750 mL of methanol, washed with water, and dried at 60°C under vacuum (1 mm) to give 228-230 g (61-62%) of 8-*n*-butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one, mp 140-141°C (Note 4).

B. 9-*n*-Butyl-1,2,3,4,5,6,7,8-octahydroacridine. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, glass stopper, and a reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler is flushed with nitrogen and then charged with 17.0 g (0.22 mol) of ammonium

acetate, 82 g (0.41 mol) of cupric acetate monohydrate (Note 5), and 200 mL of glacial acetic acid. The mixture is stirred and heated at reflux for 15 min under a static atmosphere of nitrogen. The resulting solution is allowed to cool below reflux and 53 g (0.20 mol) of 8-*n*-butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one is added in several portions. The blue-green reaction mixture is then refluxed under nitrogen for 3 hr with efficient stirring to control foaming. The mixture is allowed to cool to room temperature and then chilled in an ice bath for 3 hr. The precipitated cuprous acetate is collected by vacuum filtration using a fritted glass funnel (medium porosity) and washed with 100 mL of acetic acid. The combined filtrates are diluted with 500 mL of water, cooled in an ice bath, and carefully neutralized by slowly adding 33.3% (w/w) aqueous sodium hydroxide (Note 6). The resulting cloudy mixture is transferred to a separatory funnel and extracted with ether (400 mL, then 2 x 200 mL). The combined ether extracts are washed successively with 140 mL of 3% aqueous sodium hydroxide and 70 mL of saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate along with 1 g of decolorizing charcoal (Norit). The solids are removed by filtration and washed with 200 mL of ether. The combined filtrates are concentrated to minimum volume with a rotary evaporator, and the residual solid is dried to a constant weight under vacuum (1 mm) to give 44.3-47.0 g (91-96%) of beige, crystalline product, mp 36-38°C. The product is further purified by adding a solution of 44.3 g of material in 90 mL of dichloromethane to a column of Woelm neutral alumina (75 x 28 mm), and eluting with an additional 300 mL of dichloromethane. The solvent is removed on a rotary evaporator to give 42.1 g (86%) of white crystalline solid, mp 41-43°C (Note 7).

C. 9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide. A 2-L, round-bottomed flask equipped with a magnetic stirrer and a reflux condenser fitted with a nitrogen inlet tube is flushed with nitrogen and charged with 790 mL of methanol, 240 mL of water, 38.0 g (0.16 mol) of purified 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine, 28.5 g (0.34

mol) of sodium bicarbonate, and 72.0 g (0.12 mol) of Oxone® (Note 8). The suspension is stirred under nitrogen at 45-50°C for 24 hr (Note 9). The mixture is cooled to room temperature, filtered, and the filtercake is washed with methanol (2 x 50 mL). The methanol is removed from the combined filtrates with a rotary evaporator, and the resulting mixture is extracted with dichloromethane (3 x 100 mL). The combined extracts are washed with water (2 x 50 mL) and dried over magnesium sulfate. The drying agent is removed by filtration, the filtrate is concentrated with a rotary evaporator, and the residual solid is dried under vacuum (0.1-0.5 mm) to give 40.0 g (99%) of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide as a cream colored solid, mp 92-94°C (Notes 10, 11, and 12).

D. 9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol. Crude 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide (38.9 g, 0.15 mol) is placed in a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, glass stopper, and a reflux condenser fitted with a nitrogen inlet tube, and a 500-mL addition funnel. Acetic anhydride (300 mL) is placed in the addition funnel, deaerated by sparging with helium for 30 min, and then added rapidly to the nitrogen-purged reaction flask. The reaction mixture is stirred and heated in a 100-110°C oil bath for 2 hr. The reflux condenser is replaced by a simple distillation head and approximately 280 mL of acetic anhydride is removed by distillation at water-aspirator pressure (25-35 mm). To the brown residue is added 470 mL of 3 M aqueous hydrochloric acid, and the resulting mixture is refluxed under nitrogen for 1.5 hr. The mixture is allowed to cool to room temperature, chilled in an ice bath, and made alkaline (pH 12-13) by slowly adding about 550 mL of cold 4 M aqueous sodium hydroxide. The resulting cloudy mixture is extracted with chloroform (3 x 150 mL) and the combined extracts are dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated to dryness with a rotary evaporator. The brown residue is recrystallized from 75 mL of ethyl acetate, and the collected product is recrystallized

again from 50 mL of ethyl acetate (Note 13) to give 25.9 g (67%) of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol as a light beige solid, mp 107-109°C (Note 14).

2. Notes

1. Cyclohexanone (99.8%) was obtained from Aldrich Chemical Company, Inc. and was used without purification.

2. Certified grade potassium hydroxide (86.6%) from Fisher Scientific was used.

3. Pentanal (99%) was obtained from Aldrich Chemical Company, Inc., redistilled under a static atmosphere of nitrogen (bp 103°C), and used immediately.

4. The product has the following spectroscopic properties: ^1H NMR (300 MHz, CDCl_3) δ : 0.89 (t, 3 H, $J = 6$, CH_3), 1.1-2.3 (m, 23 H, CH_2 , CH), 2.44 (m, 1 H, CH_2), 2.72 (s, 1 H, OH); IR (KBr) cm^{-1} : 3413 (s), 2931 (s), 2857 (s), 1703 (s), 1455 (m), 1406 (m), 1378 (m), 1352 (m), 1285 (m), 1267 (m), 1206 (m), 1140 (m), 968 (m), 931 (m); mass spectrum m/z (relative abundance, 70 eV): 264 (M^+ , 10), 167 (85), 166 (100). The submitters report that a second recrystallization gives analytically pure material, mp 141-142°C. Anal. Calcd for $\text{C}_{17}\text{H}_{28}\text{O}_2$: C, 77.22; H, 10.67. Found: C, 77.34; H, 10.51.

5. Ammonium acetate (99+%) and copper(II) acetate monohydrate (98+%) were obtained from Aldrich Chemical Company, Inc.

6. Approximately 470 mL of sodium hydroxide was required to reach a final pH of 8-9. A lower pH leads to extraction of acetic acid, whereas higher pH (10) causes the formation of a white precipitate that makes a phase separation difficult during extraction.

7. The product is pure by thin-layer chromatographic analysis (Alumina GF Uniplat from Analtec, Inc., 1:1 ethyl acetate:hexane solvent, $R_f = 0.79$) and ^1H NMR

analysis. The product has the following spectroscopic properties: ^1H NMR (300 MHz, CDCl_3) δ : 0.96 (t, 3 H, $J = 6$, CH_3), 1.42 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.7-1.9 (m, 8 H, H2, H3, H6, H7), 2.49 (m, 2 H, ArCH_2), 2.68 (m, 4 H, ArCH_2), 2.85 (m, 4 H, ArCH_2); IR (neat) cm^{-1} : 2932 (s), 2858 (s), 1565 (m), 1438 (m), 1409 (m), 1246 (w); mass spectrum, m/z (relative abundance 70, eV): 243 (M^+ , 51), 228 (6), 214 (16), 201 (64), 200 (56), 186 (100). The submitters obtained an analytically pure sample by bulb-to-bulb distillation of the initial beige product. Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{N}$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.58; H, 10.07; N, 5.40.

8. Oxone®, the Du Pont Company trade name for potassium peroxymonosulfate, has the composition $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$, and was purchased from Aldrich Chemical Company, Inc.

9. Oxidation may be monitored by thin-layer chromatography (Alumina GF Uniplat, 1:1 ethyl acetate:hexane). The R_f values of the N-oxide product and starting material are 0.30 and 0.79 respectively (Note 7).

10. The submitters report obtaining 39 g (96%) of pale yellow product, mp 89-92°C, when the beige starting material from Part B, mp 36-39°C, was used without further purification. The checkers, however, obtained only an 80% yield of N-oxide, mp 87-91°C, when crude starting material was used.

11. The product is sufficiently pure to be used directly in Part D, but may be further purified by recrystallization from ethyl acetate:hexane (1:6) to give colorless material, mp 99-101°C. The product has the following spectral properties: ^1H NMR (300 MHz, CDCl_3) δ : 0.97 (t, 3 H, $J = 6$, CH_3), 1.42 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.7-1.9 (m, 8 H, H2, H3, H6, H7), 2.53 (m, 2 H, 9-CH_2), 2.69 (m, 4 H, H1, H8), 2.97 (m, 4 H, H4, H5); IR (KBr) cm^{-1} : 2942 (s), 2857 (s), 1477 (m), 1444 (m), 1424 (m), 1398 (m), 1350 (m), 1322 (m), 1286 (s), 1236 (m), 1096 (s).

12. The submitters provided the following alternative procedure for conducting the oxidation with m-chloroperoxybenzoic acid (MCPBA) in place of Oxone®: Into a 1-

L, round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and a 250-mL addition funnel are placed 56.3 g (0.26 mol) of MCPBA (80%) and 350 mL of dichloromethane. The suspension is stirred and a solution of 38.0 g (0.16 mol) of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine in 120 mL of dichloromethane is added rapidly (exotherm). When the reaction mixture ceases to boil gently from the heat of reaction, it is heated to extend the reflux period to a total of 2.5 hr. The reaction mixture is cooled to room temperature, extracted with 0.5 M aqueous sodium hydroxide (4 x 450 mL), and dried over anhydrous sodium sulfate. The drying agent is removed by filtration, the filtrate is concentrated with a rotary evaporator, and the residual solvent is removed at 0.1 mm pressure to afford 40 g (99%) of yellow crystalline product, mp 96-100°C.

13. For both recrystallizations, the solid is taken up in boiling ethyl acetate, rapidly filtered, and the filtrate is allowed to cool slowly to room temperature. It then is stored at -5°C overnight in a refrigerator prior to collecting the crystals.

14. The product ($R_f = 0.47$) contains a trace of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine ($R_f = 0.79$) by thin-layer chromatographic analysis (Alumina GF Uniplat, 1:1 ethyl acetate:hexane). The checkers chromatographed a 10-g sample on a Woelm neutral alumina column (75 x 28 mm) using 300 mL of warm ethyl acetate as eluent to give 9.2 g of colorless product, mp 107-109°C. The original and chromatographed products have identical spectroscopic properties: ^1NMR (300 MHz, CDCl_3) δ : 0.96 (t, 3 H, $J = 7$, CH_3), 1.41 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.7-1.9 (m, 6 H, H_2 , H_6 , H_7), 2.03 (m, 1 H, H_3), 2.27 (m, 1 H, H_3), 2.50 (m, 2 H, 9- CH_2), 2.70 (m, 4 H, H_1 , H_8), 2.84 (m, 2 H, H_5), 4.63 (m, 1 H, H_4), 4.76 (s, 1 H, OH); IR (KBr) cm^{-1} : 3174 (s, br), 2942 (s), 2713 (m), 1569 (s), 1432 (s), 1407 (s), 1377 (m), 1338 (s), 1307 (s), 1253 (m), 1216 (m), 1169 (m), 1155 (s), 1094 (s), 1081 (s), 1005 (s), 962 (s), 939 (m), 893 (m). The submitters obtained an analytical sample, mp 104-105°C, by recrystallization from

ethyl acetate and drying for 6 hr at room temperature (0.1 mm). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.81, H, 9.53, N, 5.19.

3. Discussion

Taken together, Steps A and B of this procedure describe the most expedient, large scale approach to 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine, which is prepared in about 60% overall yield from inexpensive starting materials. This heterocycle is an important building block for "hexagonal lattice" receptors, which are relatively rigid, planar hosts for metal ions and organic molecules.²

Several methods exist for preparing pyridines that are annelated to nonaromatic rings in the [b,e] positions,³⁻⁶ but most do not also introduce an alkyl group in the 4-position. n-Butyl groups are found to lend solubility to higher molecular weight hexagonal lattice receptors. Step A of this procedure is a modification of the method of Tilichenko, who has reported the condensation of cyclohexanone with various aldehydes.⁷ The reaction involves the following sequence: aldol condensation to form 2-pentylidenecyclohexanone, Michael addition of cyclohexanone enolate, and intramolecular aldol condensation of the resulting 1,5-diketone. Many aldol products are formed and the yield of keto alcohol depends strongly on: 1) reaction temperature; 2) use of a large excess of cyclohexanone; and 3) prolonged addition of the aldehyde. The ease of product isolation is particularly dependent on its crystallinity and solubility.

If a substituent is not required in the 4-position of the new pyridine ring, then viable alternatives to the current procedure include trimethylhydrazone-salt pyrolysis⁵ and various methods for condensing ketones or enamines with formaldehyde or methyleneammonium salts.^{4a,1,6d} The latter methods often involve isolation of the intermediate 1,5-diketone, which is condensed with ammonia or

ammonium salts to form the pyridine ring,^{4b-d,f} The yield of this cyclization is limited by disproportionation of the intermediate dihydropyridine.⁸ Hydrazine^{4e} or hydroxylamine^{2a,4a} may also be used, but yields are similar to those obtained with ammonium acetate in acetic acid. The cupric acetate/ammonium acetate method described in Step B nearly quantitatively gives annelated pyridines from various 1,5-diketone equivalents.⁸ Cupric acetate appears to be the oxidant of choice for intercepting dihydropyridines before disproportionation can occur.

Step C describes a method for oxidizing a pyridine to its N-oxide with Oxone® (potassium hydrogen persulfate). The more traditional oxidant, m-chloroperoxybenzoic acid (MCPBA), works equally well, but the availability of 80-85% pure MCPBA is now limited. Pyridine N-oxides may also be prepared with hydrogen peroxide in acetic acid,^{9,10} but reaction time is variable and removal of acetic acid is inconvenient for large scale preparations. Potassium hydrogen persulfate (Oxone®) is an inexpensive alternative to MCPBA in many oxidation reactions.¹¹ The oxidation procedure given here avoids the formation of volatile peroxides, which occurs in ketone-catalyzed N-oxidation of pyridine by persulfate.^{11b,e} A 50% excess of Oxone® is used, assuming 100% activity. The submitters used Oxone® of 67-68% purity by iodometric titration. Less oxidant leads to incomplete reaction or inconveniently long reaction times.

Synthesis of annelated polypyridines or hexagonal lattice receptors from 1,2,3,4,5,6,7,8-octahydroacridines requires oxidative functionalization of the 4-position (CH₂ group bonded to the pyridine 2-position). In Step D this is accomplished by "Katada" or "Boekelheide" rearrangement of the N-oxide. This general reaction is commonly used for selective oxidation of alkylated pyridines although the mechanism for conversion of the acetylated N-oxide to the 2-acetoxyalkylpyridine has not been fully elucidated.¹² The current procedure reflects an empirical finding that deoxygenation of the acetic anhydride prior to addition results in slightly higher yields.

Condensation of 2-alkylpyridines with benzaldehyde, followed by ozonolysis of the benzylidene intermediate is a general, alternative route to 2-oxoalkylpyridines.¹³ The N-oxide rearrangement described here is superior when monofunctionalization is required, because condensation of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine with 1 equivalent of benzaldehyde gives a mixture of monobenzylidene and dibenzylidene derivatives.² Recent work by Tilichenko has shown that 1,5 diketones may be converted to monobenzylidene derivatives before forming the pyridine ring,¹⁴ but overall yields are lower than for the current procedure.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol: 4-Acridinol, 9-butyl-1,2,3,4,5,6,7,8-octahydro- (11); (99922-91-5)

8-n-Butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one: 5,9-Methanobenzocycloocten-11-one, 10-butyldodecahydro-4a-hydroxy- (8,9); (24133-22-0)

Cyclohexanone (8,9); (108-94-1)

Pentanal: Valeraldehyde (8); Pentanal (9); (110-62-3)

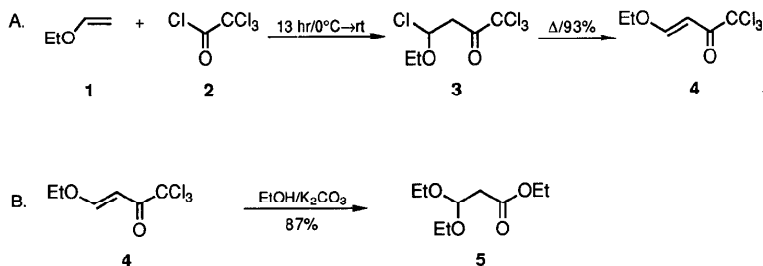
9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine: Acridine, 9-butyl-1,2,3,4,5,6,7,8-octahydro- (11); (99922-90-4)

Ammonium acetate: Acetic acid, ammonium salt (8,9); (631-61-8)

Cupric acetate monohydrate: Acetic acid, copper(2+) salt, monohydrate (8,9); (6046-93-1)

Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate (9); (37222-66-5)

**SYNTHESIS OF ALKYL PROPANOATES BY A HALOFORM REACTION OF
A TRICHLORO KETONE: PREPARATION OF ETHYL
3,3-DIETHOXYPROPANOATE
(Propanoic acid, 3,3-diethoxy-, ethyl ester)**



Submitted by L. F. Tietze, E. Voss, and U. Hartfiel.¹

Checked by Daniel Romo and Albert I. Meyers.

1. Procedure

A. *1,1,1-Trichloro-4-ethoxy-3-buten-2-one*, **4**.² A 500-mL, two-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, nitrogen inlet and magnetic stirring bar is charged with trichloroacetyl chloride, **2** (173 g, 0.96 mol) (Note 1). Under nitrogen the flask is cooled with an ice bath to 0°C and ethyl vinyl ether (137 g, 181 mL, 1.90 mol, Note 2) is added within 1 hr to the well-stirred mixture. Stirring is continued for 12 hr allowing the mixture to warm to room temperature without removing the cooling bath (Note 3). The addition funnel is replaced by a short Vigreux column and excess ethyl vinyl ether is removed at 20°C under reduced pressure (20 mm). The bath-temperature is raised (to approx. 140°C)

under reduced pressure (20 mm) to start elimination of hydrogen chloride, which is accompanied by formation of a deep black color and requires 1-2 hr for completion. Distillation of the residue under reduced pressure affords 193 g (92%) of **4**,³ as a bright yellow oil which fades to pale yellow on standing, bp 116-118°C/13 mm, n_D^{24} 1.5129 (Notes 4,5).

B. Ethyl 3,3-diethoxypropanoate, 5. A 500-mL, two-necked, round-bottomed flask equipped with magnetic stirring bar, reflux condenser with drying tube, and 250-mL pressure equalizing addition funnel is charged with dry ethanol (200 mL, 3.4 mol) and anhydrous potassium carbonate (12 g, 87 mmol) and cooled with an ice/water bath. The addition funnel is charged with 1,1,1-trichloro-4-ethoxy-3-buten-2-one, **4** (200 g, 0.92 mol) and the addition is performed with stirring during 30 min. Stirring is continued for 10 hr at room temperature, petroleum ether or pentane (300 mL) is added, and the potassium carbonate is filtered off. After concentration under reduced pressure the residue is distilled through a short Vigreux column, to yield 153 g (87%) of **5**, bp 92-95°C/15 mm, n_D^{24} 1.4117 (Notes 6, 7).

2. Notes

1. Trichloroacetyl chloride (obtained from Fluka Chemical Corporation) was distilled immediately before use.

2. Ethyl vinyl ether (obtained from Fluka Chemical Corporation) was used from a freshly opened bottle containing a stabilizer (0.1% diethylaniline) without purification. The stabilizer seems to be important (see Note 7).

3. An exothermic reaction was observed after removing the ice bath.

4. Distillation should not be performed at a lower pressure.

5. The synthesis of **4** can be carried out on a large scale: a run using 1.8 kg of trichloroacetyl chloride gave **4** in 97% yield. The spectral properties are as follows: IR (neat) cm^{-1} : 2990 (C-H), 1710 (C=O), 1600 (C=C), 835 (C-Cl); ^1H NMR (60 MHz, CDCl_3) δ : 1.38 (t, 3 H, $J = 7$, OCH_2CH_3), 4.08 (q, 2 H, $J = 7$, OCH_2CH_3), 6.13 (d, 1 H, $J = 12.4$, 3-H), 7.87 (d, 1 H, $J = 12.4$, 4-H).

6. Distillation should only be performed at the indicated temperature range. Approximately 20 mL of a dark residue remains after distillation. The spectral properties are as follows: IR (neat) cm^{-1} : 2990, 2940 (C-H), 1740 (C=O), 1115, 1060 (C-O); ^1H NMR (60 MHz, CDCl_3) δ : 1.18 (t, 6 H, $J = 7$, OCH_2CH_3), 1.25 (t, 3 H, $J = 7$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.62 (d, 2 H, $J = 6$, 2-H), 3.30-3.80 (2 AB - systems, 4 H, 2 OCH_2CH_3), 4.13 (q, 2 H, $J = 7$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.93 (t, 1 H, $J = 6$, 3-H).

7. In a similar way, methyl 3,3-dimethoxypropanoate can be prepared using trichloroacetyl chloride and methyl vinyl ether as starting materials. However, in this case, using methyl vinyl ether without a stabilizer, it is necessary to perform the reaction in the presence of pyridine; otherwise extensive polymerization of the vinyl ether takes place.

Procedure: A 1000-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, intensive condenser (cryostat temp., -5°C) with nitrogen inlet, and mechanical stirrer, is charged with **2** (270 g, 1.48 mol); pyridine (117 g, 1.48 mol) is added within 15 min under vigorous stirring at room temperature. Under nitrogen, the flask is cooled with an ice bath to -10°C and liquid methyl vinyl ether (112 g, approx. 145 mL, 1.93 mol) is added through a coolable addition funnel (approx. -10°C) within 30 min to the well-stirred mixture. Stirring is continued for 12 hr, allowing the mixture to warm to room temperature without removing the cooling bath. After addition of water (250 mL) and extraction with diethyl ether (2 x 200 mL), the combined organic layers are washed with brine (2 x 50 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Distillation

(20-cm Vigreux column) of the residue under reduced pressure affords 267 g (88%) of 1,1,1-trichloro-4-methoxy-3-buten-2-one as a colorless liquid, bp 102°C/10 mm, n_D^{20} 1.5238. The spectral properties are as follows: IR (neat) cm^{-1} : 2940, 2840 (C-H), 1710 (C=O), 1600 (C=C); ^1H NMR (60 MHz, CDCl_3) δ : 3.80 (s, 3 H, OCH_3), 6.03 (d, 1 H, $J = 12$, 3-H), 7.77 (d, 1 H, $J = 12$, 4-H). Solvolysis of 1,1,1-trichloro-4-methoxy-3-buten-2-one with methanol to give methyl 3,3-dimethoxypropanoate can be performed according to the procedure given for 5.

3. Discussion

The synthesis of ethyl 3,3-diethoxypropanoate, 5, described here implies acylation of an enol ether followed by a haloform reaction. The procedure is superior to other methods, which afford mixtures of acetals and acrylates,⁴ give only moderate yields,^{5,6,7} require the troublesome use of ketene⁸ or expensive ethyl propiolate,^{9,10,11} need palladium(II) catalysis,¹² or equipment for electrochemical reactions.¹³

Ethyl 3,3-diethoxypropanoate, 5, is the stable, protected derivative of the unstable 3-formylpropanoate. It can be stored at room temperature for several months without decomposition. It is a useful starting material, especially for the synthesis of heterocycles such as coumarins,¹⁴ isoxazoles,¹⁵ pyrimidines,¹⁶ porphyrins,¹⁷ and thiadiazines.¹⁸ Also spermine metabolites,¹⁹ steroids,²⁰ herbicides,²¹ anti-hypertensives,²² photographic sensitizers,²³ cephalosporins,²⁴ lycopodium alkaloids,²⁵ nucleic acids,⁵ and pentaerythritol²⁶ as well as related alcohols can be obtained from 5. Thus ester 5 can be reduced to the corresponding alcohol which yields 3-hydroxypropanal with acidic conditions;²⁶ elimination of ethanol gives 3-ethoxyacrylate.²⁷ Of great interest is also the formylation of 5 to give ethyl 2-formyl-3-oxopropanoate or, starting from methyl 3,3-dimethoxypropanoate, methyl 2-formyl-3-

oxopropanoate.^{10,28} The latter compound has been used in the synthesis of iridoids,²⁸ ipecacuanha alkaloids,²⁹ 1,4-dihydropyridines,²⁹ NADH analogues,³⁰ dihydropyrans,³¹ and branched amino sugars.³²

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 3,3-diethoxypropanoate: Propanoic acid, 3,3-diethoxy-, ethyl ester (9);
(10601-80-6).

1,1,1-Trichloro-4-ethoxy-3-buten-2-one: 3-Buten-2-one, 1,1,1-trichloro-4-ethoxy- (11);
(83124-74-7)

Trichloroacetyl chloride: Acetyl chloride, trichloro- (8,9); (76-02-8)

Ethyl vinyl ether: Ether, ethyl vinyl (8); Ethene, ethoxy- (9); (109-92-2)

Methyl 3,3-dimethoxypropanoate: Propanoic acid, 3,3-dimethoxy-, methyl ester (9);
(7424-91-1)

Methyl vinyl ether: Ether, methyl vinyl (8); Ethene, methoxy- (9); (107-25-5)

1,1,1-Trichloro-4-methoxy-3-buten-2-one: 3-Buten-2-one, 1,1,1-trichloro-4-methoxy-,
(E)- (12); (116140-91-1)

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- 2509R Preparation and Diels-Alder Reaction of a Reactive, Electron-Deficient Heterocyclic Azadiene: Dimethyl 1,2,4,5-Tetrazine-3,6-Dicarboxylate. 1,2-Diazine and Pyrrole Introduction.
D. L. Boger, J. S. Panek, and M. Patel, Department of Chemistry, Purdue University, West Lafayette, IN 47907
- 2527 (-)-(1S,4R)-Camphanoyl Chloride.
D. Kappes and H. Gerlach, Laboratorium für Organische Chemie, Universität Bayreuth, Postfach 101251, D-8580 Bayreuth, West Germany
- 2539* 1-Phenyl-2,3,4,5-Tetramethylphosphole.
P. J. Fagan and W. A. Nugent, E. I. du Pont de Nemours & Co., Inc. Central Research & Development Department, Experimental Station, Wilmington, DE 19898
- 2541* Synthesis of Furans via Rhodium(II) Acetate Catalyzed Reaction of Acetylenes with α -Diazocarbonyls.
H. M. L. Davies, W. R. Cantrell, Jr., and J. S. Baum, Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109
- 2542* Nickel-Catalyzed Silylolation of Allylic Dithioacetals: (E,E)-Trimethyl(4-Phenyl-1,3-butadienyl)silane.
Z.-J. Ni and T.-Y. Luh, Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong
- 2545* α -Acetylenic Esters from α -Acylmethylenephosphoranes: Ethyl 4,4,4-Trifluorotetrolate.
B. C. Hamper, Monsanto Agricultural Co., 800 N. Lindburgh Blvd., St. Louis, MO 63167
- 2546* 4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheptacosane (Triaza-21-crown-7).
K. E. Krakowiak and J. S. Bradshaw, Department of Chemistry, Brigham Young University, Provo, UT 84602
- 2547 Methoxycarbonylmethylation of Aldehydes via Siloxycyclopropanes: Methyl 3,3-Dimethyl-4-oxobutanoate.
H.-U. Reissig, I. Reichelt, and T. Kunz, Institut für Organische Chemie, Technische Hochschule Darmstadt, 6100 Darmstadt, Petersenstr. 22, Federal Republic of Germany
- 2548* Tetrahydro-3-benzazepin-2-ones: Lead Tetraacetate Oxidation of Isoquinoline Enamides.
G. R. Lenz and R. A. Lessor, Health Care R & D, The BOC Group, Inc., 100 Mountain Ave., Murry Hill, NJ 07974
- 2549* 3,4-Diethylpyrrole and Octaethylporphyrin.
J. L. Sessler, A. Mozaffari, and M. R. Johnson, Department of Chemistry, The University of Texas at Austin, Austin, TX 78712-1167
- 2553* 9-Borabicyclo[3.3.1]nonane Dimer.
J. A. Soderquist and A. Negron, Department of Chemistry, University of Puerto Rico, Rio Piedras Campus, Rio Piedras, Puerto Rico 00931

- 2555* Iodolactamization: 8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one.
S. Knapp and F. S. Gibson, Department of Chemistry, Rutgers, The
State University of New Jersey, New Brunswick, NJ 08903
- 2556 Substitution Reactions of 2-Benzenesulfonyl Cyclic Ethers:
Tetrahydro-2-(phenylethynyl)-2H-pyran.
D. S. Brown and S. V. Ley, Department of Chemistry, Imperial
College, London SW7 2AY, United Kingdom
- 2558* Spiroannulation via Organobis(cuprates): 9,9-
Dimethylspiro[4.5]decan-7-one.
P. A. Wender, A. W. White, and F. E. McDonald, Department of
Chemistry, Stanford University, Stanford, CA 94305
- 2560* 2-Methyl-1,3-cyclopentanedione.
P. G. Meister, M. R. Sivik, and L. A. Paquette, Department of
Chemistry, The Ohio State University, Columbus, OH 43210
- 2561 Dialkyl Mesoxalate by Ozonolysis of Dialkyl Benzalmalonates:
Preparation of Dimethyl Mesoxalate.
L. F. Tietze and M. Bratz, Institut für Organische Chemie der Georg
August Universität, Tammannstrasse 2, D-3400 Göttingen, Federal
Republic of Germany
- 2562 Synthesis of 2-Substituted Naphthalenediol Derivatives Utilizing
Chromium Carbene Complexes: 1-Acetoxy-2-butyl-4-methoxynaphthalene.
J. M. Timko and A. Yamashita, The Upjohn Company,
Kalamazoo, MI 49001
- 2564 (S)-(-)- and (R)-(+)-1,1'-Bi-2-naphthol.
R. J. Kazlauskas, Department of Chemistry, McGill University,
Montreal, PQ H3A2K6, Canada
- 2565 (R)-(-)-10-Methyl-1(9)-octal-2-one.
G. Revial and M. Pfau, CNRS, ESPCI, Unite de Chimie Organique 10,
rue Vauquelin, 75213 Paris Cedex 05, France
- 2566 Titanium Mediated Addition of Silyldienolethers to Electrophilic
Glycine: A Short Synthesis of 4-Ketopipicolinic Acid Hydrochloride.
C. Muhlemann, P. Hartmann and J.-P. Obrecht, SOCAR AG
Überlandstrasse 138, 8600 Dübendorf, Switzerland
- 2567 Tris(trimethylsilyl)silane.
J. Dickhaut and B. Giese, Institute of Organic Chemistry, University
of Basel, St. Johannis-Ring 19, CH-4056 Basel, Switzerland
- 2568 Synthesis of Primary Amines via the Reaction of Organoboranes with
Trimethylsilyl Azide in Neutral Medium: 2-exo-Norbornyl Amine.
G. W. Kabalka and Z. Wang, Department of Chemistry, University of
Tennessee, Knoxville, TN 37996

- 2569 1,2-Addition of a Functionalized Zinc and Copper Organometallic (RCu(CN)ZnI) to an α,β -Unsaturated Aldehyde.
M. C. P. Yeh, H. G. Chen, and P. Knochel, Department of Chemistry, University of Michigan, Ann Arbor, MI 48109
- 2570 N-[(Benzyloxy)carbonyl]-L-vinylglycine Methyl Ester.
M. Carraso, R. J. Jones, S. Kamel, H. Rapoport, and T. Truong, Department of Chemistry, University of California, Berkeley, CA 94720
- 2572 R,R-1,2-Diphenyl-1,2-ethanediol (Stilbene Diol).
B. H. McKee, D. G. Gilheany, and K. B. Sharpless, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139
- 2574 4-Methoxy-4'-nitrobiphenyl.
J. K. Stille, A. M. Echavarren, R. M. Williams, and J. A. Hendrix, Department of Chemistry, Colorado State University, Fort Collins, CO 80523
- 2575 2,2'-Dimethoxy-6-formylbiphenyl.
A. I. Meyers and M. E. Flanagan, Department of Chemistry, Colorado State University, Fort Collins, CO 80523

CUMULATIVE AUTHOR INDEX

FOR VOLUMES 65, 66, 67, 68, AND 69

This index comprises the names of contributors to Volumes 65, 66, 67, 68, and 69 only. For authors to previous volumes, see either indices in *Collective Volumes I through VII* or the single volume entitled *Organic Syntheses, Collective Volumes, I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner

Abrams, S. R., 66, 12
 Adger, B. M., 67, 187
 Åkermærk, B., 68, 109
 Akutagawa, S., 67, 20, 33
 Almond, M. R., 66, 132
 Andell, O. S., 68, 148
 Anderson, F., 67, 121
 Anelli, P. L., 69, 212
 Aoyama, T., 68, 1
 Asirvatham, E., 69, 188
 Aslamb, M., 65, 90
 Augolli, C. E., 68, 210

 Baba, S., 66, 60
 Bäckvall, J. E., 67, 105; 68, 148;
 69, 38
 Bankston, 66, 180
 Barrett, A. G. M., 68, 8
 Bell, T. W., 69, 226
 Bercaw, J. E., 65, 42
 Bergman, J., 65, 146
 Bergman, R. G., 65, 42
 Berney, D., 69, 55
 Blaszcak, L. C., 68, 104
 Block, E., 65, 90
 Døger, D. L., 65, 32, 98; 66, 142
 Boeckman, R. K., Jr., 66, 194
 Boes, M., 67, 52, 60
 Bou, A., 65, 68
 Braxmeier, H., 65, 159
 Brotherton, C. E., 65, 32
 Brown, C. A., 65, 224
 Brown, J. M., 68, 64
 Brown, M. J., 68, 182

Büchi, G. H., 66, 29
 Bunnelle, W. H., 69, 89
 Buter, J., 65, 150

 Cabezas, J., 69, 120
 Cacchi, S., 68, 138
 Calzada, J., 69, 120
 Casy, G., 67, 193
 Celerier, J. P., 67, 170
 Cha, D. D., 68, 32
 Chang, T. C. T., 66, 95
 Cho, Y.-M., 69, 226
 Coghlan, M. J., 67, 157
 Corey, E. J., 65, 166
 Crisp, G. T., 68, 116
 Crow, R., 69, 80

 Danheiser, R. L., 66, 1, 8, 14; 68, 32
 Davidsen, S. K., 65, 119
 Davis, F. A., 66, 203; 69, 154, 158
 Deardorff, D. R., 67, 114
 Deloisy-Marchalant, E., 67, 170
 de Meijere, A., 69, 144, 148
 Dent, W., 67, 133
 Deprés, J.-P., 68, 41
 Dhanak, D., 68, 8
 Dhawan, B., 68, 238
 Dickman, D. A., 67, 52, 60
 Duncan, M. P., 68, 175
 Dupuis, J., 65, 236

 Eberle, M., 69, 19
 Eliel, E. L., 65, 215
 Enders, D., 65, 173, 183

- Engler, A., 66, 37
Escudero, J., 69, 199
Evans, D. A., 68, 77, 83
Evans, P. L., 68, 64
- Fahlbusch, K.-G., 69, 31
Falmagne, J. B., 60, 190
Fey, P., 65, 173, 183
Fink, D. M., 66, 1, 8, 14
Firestone, A., 69, 226
Fishbein, P. L., 69, 205
Flann, C. J., 68, 188
Forth, M. A., 67, 187
Fouquey, C., 67, 1
Fowler, K. W., 65, 108
Fox, C. M. J., 66, 108
Frye, S. V., 65, 215
Fujisawa, T., 65, 116, 121
Fujita, M., 69, 44
Fujita, T., 67, 44
Furuta, K., 67, 76
- Gadwood, R. C., 67, 210
Gage, J. R., 68, 77, 83
Gatto, V. J., 68, 227
Georg, G. I., 65, 32
Ghosez, L., 69, 199
Giese, B., 65, 236; 69, 66
Goel, O. P., 67, 69
Gokel, G. W., 68, 227
Goodwin, G. B. T., 65, 1
Graboski, G. G., 68, 8
Greene, A. E., 68, 41
Grieco, P. A., 68, 206
Groninger, K. S., 69, 66
Gross, A. W., 65, 166
Gutsche, C. D., 68, 234, 238, 243
- Haese, W., 65, 26
Halligan, N. G., 68, 104
Hanessian, S., 65, 243
Hanson, S., 68, 109
Hartfiel, U., 69, 238
Healy, K., 69, 226
Hegedus, L. S., 65, 140
Hemperly, S. B., 68, 92
Heumann, A., 68, 109
Hirst, G. C., 69, 169
Hiyama, T., 69, 44
- Holmes, A. B., 65, 52, 61
Hobbs, F. W., Jr., 66, 52
Hooz, J., 69, 120
Hormi, O., 66, 173
Hudlicky, T., 67, 121, 202
Hsiao, C.-N., 65, 135
Huang, Z., 66, 211
Hui, R., 69, 114
- Imwinkelried, R., 65, 230; 67, 180
Iqbal, M., 68, 234
Ishida, N., 69, 96
Ito, Y., 69, 96
Iwanaga, K., 67, 76
- Jacques, J., 67, 1
Jadhav, P. K., 65, 224
Jaekel, F., 69, 144
James, A. P., 68, 64
Jones, G. E., 65, 52
Juntunen, S. K., 68, 148
- Kagan, H. B., 68, 49
Kalaritis, P., 69, 10
Katagiri, T., 67, 44, 48
Kawada, K., 69, 129
Kellogg, R. M., 65, 150
Kendrick, D. A., 65, 52
Kesten, S., 67, 69
Kiedrowski, G. v., 69, 31
Kim, G., 69, 72
King, A. O., 66, 67
Kipphardt, H., 65, 173, 183
Kobayashi, Y., 69, 106
Koppenhoefer, B., 66, 151, 160
Kraus, G. A., 67, 202
Kresze, G., 65, 159
Krolls, U., 67, 69
Krolski, M. E., 67, 202
Kuhlmann, H., 65, 26
Kumda, M., 69, 96
Kume, F., 65, 215
Kumobayashi, H., 67, 33
Kuwaitima, I., 65, 17; 66, 43, 87
- Labadie, J. W., 67, 86
Lal, G. S., 69, 158
Larson, G. L., 67, 125
Larson, S. D., 68, 206

- Lassalle, G., **69**, 173
 Lawrence R. M., **69**, 1
 Lee, V., **69**, 72
 Le Gal, J. Y., **65**, 47
 Leonis, M., **68**, 238
 Ley, S. V., **66**, 108
 Lhommet, G., **67**, 170
 Liese, T., **69**, 144, 148
 Lin, H.-S., **67**, 157, 163
 Lindsay Smith, J. R., **67**, 222
 Lipshutz, B. H., **69**, 80
 Liu, J., **69**, 226
 Lombardo, L., **65**, 81
 Loudon, G. M., **66**, 132
 Ludwig, R., **69**, 226
 Lynch, J. E., **65**, 215

 Macdonald, J. E., **66**, 194
 Madan, P., **69**, 1
 Maitte, P., **67**, 170
 Malone, T. C., **68**, 188
 Martin, S. F., **65**, 119
 Maruoka, K., **66**, 185; **67**, 176
 Mash, E. A., **68**, 92
 Masuda, T., **66**, 22
 McCann, S. F., **68**, 182
 McGuire, M. A., **65**, 140
 McKeer, L. C., **67**, 222
 McLaughlin, M. L., **68**, 220
 McLoughlin, J. I., **68**, 14
 Meth-Cohn, O., **68**, 155
 Meyers, A. I., **67**, 52, 60; **69**, 55
 Mickel, S. J., **65**, 135
 Midland, M. M., **68**, 14
 Miele, L. R., **67**, 125
 Miller, M. J., **65**, 135
 Miller, S. A., **67**, 210
 Miller, S. R., **68**, 227
 Mimura, S., **66**, 22
 Missbach, M., **69**, 19
 Miyaura, N., **68**, 130
 Montanari, F., **69**, 212
 Montes de Lopez-Cepero, I., **67**, 125
 Mook, R., Jr., **66**, 75
 Moore, H. W., **69**, 205, 220
 Morera, E., **68**, 138
 Moretti, R., **69**, 80
 Mori, H., **68**, 56
 Mori, K., **69**, 50

 Mori, S., **68**, 1
 Moriarty, R. M., **68**, 175
 Mukaiyama, T., **65**, 6
 Mullican, M. D., **65**, 98
 Munch, J. H., **68**, 243
 Munsterer, H., **65**, 159
 Musmanni, S., **69**, 120
 Myles, D. C., **67**, 114

 Nakai, S., **66**, 185
 Nakamura, E., **65**, 17; **66**, 43
 Nakamura, T., **67**, 98
 Narasaka, K., **65**, 6, 12
 Narayanan, B. S., **69**, 89
 Näsman, J. H., **68**, 162
 Negishi, E.-I., **66**, 60, 67
 Nelson, K. A., **68**, 92
 Neveu, M., **67**, 205
 Nicholas, K. M., **67**, 141
 Nix, M., **65**, 236
 Noyori, R., **67**, 20
 Nugent, W. A., **66**, 52
 Nyström, J. E., **67**, 105

 Ochiai, H., **67**, 98
 Okano, K., **66**, 14
 Olomucki, M., **65**, 47
 Ort, O., **65**, 203
 Ortar, G., **68**, 138
 Otsuka, S., **67**, 33
 Overman, L. E., **68**, 182, 188
 Oxley, P. W., **67**, 187

 Padwa, A., **67**, 133
 Panek, J. S., **66**, 142
 Paquette, L. A., **67**, 149, 157, 163;
 68, 198, 220; **69**, 173
 Parsons, P. J., **69**, 169
 Patterson, J. W., **67**, 193
 Pauley, D., **67**, 121, 205
 Pelter, M. W., **68**, 198
 Pericas, M. A., **65**, 68
 Perni, R. B., **66**, 194
 Perri, S. T., **69**, 220
 Phillips, G. W., **65**, 119
 Pine, S. H., **69**, 72
 Posner, G. H., **69**, 188
 Poulter, C. D., **66**, 211
 Poupart, M.-A., **69**, 170

- Prakash, O., **68**, 175
- Quici, S., **69**, 212
- Rambaud, M., **66**, 220
- Ranu, B. C., **67**, 205
- Regenye, R. W., **69**, 10
- Rein, T., **67**, 105; **68**, 109
- Renaldo, A. F., **67**, 86
- Rice, P., **69**, 220
- Riera, A., **65**, 68
- Rigby, H. L., **67**, 205
- Rodgers, W. B., **65**, 108
- Rosenblum, M., **66**, 95
- Rothenberger, S. D., **69**, 238
- Saha, M., **67**, 141
- Sakane, S., **67**, 176
- Samuel, O., **68**, 49
- Sand, P., **65**, 146
- Sasse, M. J., **67**, 187
- Sato, F., **69**, 106
- Sato, T., **66**, 116, 121
- Savariar, S., **68**, 32
- Schiess, M., **65**, 230
- Schmit, C., **69**, 199
- Schultze, L. M., **65**, 140
- Schurig, V., **66**, 151, 160
- Schwartz, A., **69**, 1
- Scott, L. T., **69**, 180
- Scott, W. J., **68**, 116
- Seebach, D., **65**, 230; **67**, 180; **69**, 19
- Seidler, P. F., **65**, 42
- Serratos, F., **65**, 68
- Seyed-Mahdavi, F., **69**, 148
- Seyferth, D., **69**, 114
- Shaw, A. C., **66**, 127
- Sheppard, A. C., **69**, 158
- Sher, P. M., **66**, 75
- Shioiri, T., **68**, 1
- Simms, N., **66**, 95
- Smith, G. C., **65**, 1
- Soderquist, J. A., **68**, 25
- Spitzner, D., **66**, 37
- Sporikous, C. N., **65**, 61
- Stetter, H., **65**, 26
- Stewart, D., **68**, 238
- Stier, M., **67**, 69
- Stille, J. K., **67**, 86; **68**, 116
- Stimmel, J. B., **66**, 132
- Stringer, O. D., **66**, 203
- Stryker, J. M., **65**, 42
- Suga, K., **67**, 44
- Sumpter, C. A., **69**, 180
- Suzuki, A., **68**, 130
- Sy, J., **67**, 202
- Szczepanski, S. W., **65**, 14
- Takabe, K., **67**, 44, 48
- Takahashi, T., **66**, 60, 67
- Takaya, H., **67**, 20
- Takeda, A., **66**, 22
- Tamao, K., **69**, 96
- Tamaru, Y., **67**, 98
- Tanaka, J., **67**, 44, 48
- Tani, K., **67**, 33
- Taylor, J. M., **67**, 222
- Taylor, R. J. K., **67**, 193
- Taylor, R. T., **68**, 198
- Taylor, S. J., **68**, 8
- Thomas, A. J., **66**, 194
- Thompson, E. A., **66**, 132
- Threlkel, R. S., **65**, 42
- Tietze, L. F., **69**, 31, 238
- Tomita, K., **69**, 129
- Towson, J. C., **69**, 154, 158
- Truesdale, L., **67**, 13
- Tsai, Y.-M., **66**, 1, 8, 14
- Tsuboi, S., **66**, 22
- Umemoto, T., **69**, 129
- Urabe, H., **66**
- Vågberg, J., **69**, 38
- Vaid, R. K., **68**, 175
- Van Deusen, S., **68**, 92
- Vanlierde, H., **69**, 199
- Varghese, V., **67**, 141
- Villieras, J., **66**, 220
- Vishwakarma, L. C., **66**, 203
- Vogel, D. E., **66**, 29
- Voss, E., **69**, 31, 238
- Walshe, N. D. A., **65**, 1
- Watanabe, S., **67**, 44
- Waykole, L., **67**, 149
- Webb, K. S., **69**, 180

Weismiller, M. C., **69**, 154, 158
Werley, Jr., R. T., **68**, 14
Wester, R. T., **65**, 108
Whitesell, J. K., **69**, 1
Wilson, S. R., **68**, 210
Woodside, A. B., **65**, 211
Woodward, F. E., **65**, 1

Yamada, T., **67**, 48
Yamagata, T., **67**, 33
Yamamoto, H., **66**, 185; **67**, 76, 176
Yasuda, M., **66**, 142
Yoshida, Z., **67**, 98

Zhao, S. H., **68**, 49
Ziegler, F. E., **65**, 108

**CUMULATIVE SUBJECT INDEX
FOR VOLUMES 65, 66, 67, 68, AND 69**

This index comprises subject matter for Volumes 65, 66, 67, 68, and 69. For subjects in previous volumes, see either the indices in *Collective Volumes I through VII* or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in parentheses. While the systematic name is indexed separately, it also accompanies the common name. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

Acetamide; (60-35-5), **69**, 11

Acetamide, N,N-dimethyl-, **67**, 98; **69**, 199

Acetic acid, **69**, 33, 38, 175

Acetamide, N-hydroxy-N-phenyl-, **67**, 187

Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester,
[1R (1 α ,2 β ,5 α)] , **66**, 203

Acetic acid, (diethoxyphosphinyl)-, ethyl ester; (867-13-0), **66**, 224

Acetic acid, ethenyl ester, **65**, 135

Acetic acid, (hexahydro-2H-azepin-2-ylidene)-, ethyl ester, (Z)-, **67**, 170

Acetic acid, hydrazinoimino-, ethyl ester; (53085-26-0), **66**, 149

Acetic acid, lithium salt, dihydrate, **67**, 105

Acetic acid, palladium(2+) salt, **67**, 105

Acetic acid, trifluoro-, anhydride, **65**, 12

Acetic acid, vinyl ester, **65**, 135

Acetic anhydride, **69**, 20, 229

Acetoacetylation, with diketene, **68**, 210

Acetohydroxamic acid, N-phenyl-, **67**, 187

ACETONE TRIMETHYLSILYL ENOL ETHER. SILANE, (ISOPROPENYLOXY)-
TRIMETHYL-; SILANE, TRIMETHYL[(1-METHYLETHENYL)OXY]-;
(1833-53-0), **65**, 1

Acetonitrile, purification, **66**, 101

Acetophenone; Ethanone, 1-phenyl-; (98-86-2), **65**, 6, 119

Acetophenone silyl enol ether: Silane, trimethyl[(1-phenylvinyl)oxy]-;
Silane, trimethyl[(1-phenylethenyl)oxy]-; (13/35-81-4), **65**, 12

4-ACETOXYAZETIDIN-2-ONE: 2-AZETIDINONE, 4-HYDROXY-ACETATE (ESTER):
2-AZETIDINONE, 4-(ACETYLOXY)-; (28562-53-0), **65**, 135

1-ACETOXY-4-BENZYLAMINO-2-BUTENE: 2-BUTEN-1-OL, 4-CHLORO-,
ACETATE (E)-; (34414-28-3), **67**, 105

4-Acetoxy-3-chloro-1-butene: 3-Buten-1-ol, 2-chloro-, acetate; (96039-67-7), **67**, 105

1-Acetoxy-4-chloro-2-cyclohexene, cis: 2-Cyclohexen-1-ol, 4-chloro-, acetate;
(82736-39-8), **69**, 38

1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE, cis:
PROPANEDIOIC ACID, [4-(ACETYLOXY)-2-CYCLOHEXEN-1-YL]-,
DIMETHYL ESTER, cis- (11); (82736-52-5), **69**, 38

1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE, trans:
PROPANEDIOIC ACID, [4-(ACETYLOXY)-2-CYCLOHEXEN-1-YL]-,
DIMETHYL ESTER, trans- (11); (82736-53-6), **69**, 38

1-ACETOXY-4-DIETHYLAMINO-2-BUTENE: 2-BUTEN-1-OL, 4-(DIETHYLAMINO)-,
ACETATE; (82736-47-8), **67**, 105

3-ACETOXY-5-HYDROXYCYCLOPENT-1-ENE, cis-: 4-CYCLOPENTEN-1,3-DIOL,
MONOACETATE, cis-; (60410-18-6), **67**, 114

Acetoxylation, allylic, **68**, 109

3-Acetoxy-2-nitrocyclohexyl acetate, (1R,2r,3S): 1,3-Cyclohexanediol, 2-nitro-,
diacetate (ester), (1 α ,2 β ,3 α)-; (51269-14-8), **69**, 20

Acetylene: Ethyne: (74-86-2). **65**, 61; **68**, 14

Acetylenes, arylsulfonyl-, **67**, 149

α,β -Acetylenic esters from β -chloroalkylidene malonates, **66**, 178

3-ACETYL-4-HYDROXY-5,5-DIMETHYLFURAN-2(5H)-ONE. **66**, 108, 110

N-ACETYL-N-PHENYLHYDROXYLAMINE: ACETOHYDROXAMIC ACID, N-
PHENYL; ACETAMIDE, N-HYDROXYL-N-PHENYL-; (1795-83-1), **67**, 187

ACETYLTRIMETHYLSILANE: Silane, acetyltrimethyl; (13411-48-8). **68**, 25

4-ACRIDINOL, 9-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDRO; (99922-91-5), **69**, 226

Acrylonitrile; 2-Propenenitrile; (107-13-1), **65**, 236

Acyl chlorides, preparation, **66**, 116

Acylsilanes, preparation, **66**, 18

ADDITION OF TIN RADICALS TO TRIPLE BONDS, **66**, 75

Adipic acid monomethyl ester; (627-91-8), **66**, 116, 117, 120

Alane, (E)-1-decenyldiisobutyl-, **66**, 60, 61

(S)-Alanine (L-alanine); (56-41-7), **66**, 151-153, 159

Alanine, phenyl-, L-; (63-91-2), **68**, 77

Aldehydes, preparation from carboxylic acid, **66**, 124

Aldol reaction, **65**, 6, 12

 diastereoselective, **68**, 83

Alkenylzinc reagents, **66**, 64

Alkylation, of ester enolate, **66**, 87

(R)-Alkyloxiranes, properties, **66**, 169

(R)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY, **66**, 160

ALKYNE ISOMERIZATION, **66**, 127

Allene; (463-49-0), **69**, 121

Allene, 1-methyl-1-(trimethylsilyl)-, **66**, 8, 9

Allenes, synthesis by Claisen rearrangement, **66**, 22

β -Allenic esters, conjugation by alumina, **66**, 26

ALLENYLSILANES, SYNTHESIS OF, **66**, 1

Allyl alcohol; (107-18-6), **66**, 14, 16, 21

Allyl bromide; (106-95-6), **68**, 104; **69**, 57

ALLYLCARBAMATES, **65**, 159

Allyl ester enolate (Carroll) rearrangement, **68**, 210

Allylic acetoxylation, **68**, 109

Allylmagnesium bromide; (1730-25-2), **68**, 104

(E)-3-Allyloxyacrylic acids, **66**, 33, 34

ALLYLTRIBUTYLtin: Stannane, tributyl-2-propenyl-; (24850-33-7), **68**, 104
Allyl trimethylsilyl ether, metallation, **66**, 18
Aluminate(1-), dihydrobis-2-(methoxyethanalato)-, sodium, **67**, 13
Aluminate(1-), tetrahydro-, lithium, **67**, 69
Aluminum chloride, **66**, 90
Aluminum oxide, **66**, 23
Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7), **66**, 193
Aluminum, triisobutyl, **67**, 176
Aluminum, tripropyl-; (102-67-0), **66**, 193
Amberlite IR-120 (plus), acid form; (78922-04-0), **69**, 21
Amberlyst 15 ion exchange resin, **66**, 203, 206; **69**, 159
Amino acids, determination of enantiomeric purity, **66**, 153
1-AMINO-2-METHOXYMETHYLPYRROLIDINE, (R)-(+)- (RAMP), **65**, 173
1-AMINO-2-METHOXYMETHYLPYRROLIDINE, (S)-(-)- (SAMP), **65**, 173, 183
2-Amino-1 phenyl-1,3 propanediol, (1S,2S)-(+)-: 1,3-Propanediol, 2-amino-1-phenyl;
(3306-06-7), **69**, 55
3-Aminopropylamine: 1,3-Propanediamine; (109-76-2), **65**, 224
Ammonia, **66**, 133, 135
Ammonium acetate; (631-61-8), **69**, 228
Ammonium, benzyltrimethyl-, hydroxide; (100-85-6), **68**, 56
Anisole, 2,4-dichloro-, **67**, 222
[3+3] Annulation, **66**, 4, 8, 10, 11
 α -D-Arabinohexopyranose, 2-deoxy, tetraacetate; (16750-06-4), **69**, 66
Asymmetric alkylation, **67**, 60
Asymmetric synthesis, **65**, 183, 215
of cycloalkane dicarboxylates, **67**, 76
AZA-ENE REACTION, **65**, 159

1H-Azepine, hexahydro-2-propyl-, (85028-29-1), **66**, 193
 2H-Azepine, 3,4,5,6-tetrahydro-7-methoxy-, **67**, 170
 2-AZETIDINONE, 4-(ACETYLOXY)-, **65**, 135
 2-AZETIDINONE, 4-HYDROXY-ACETATE (ESTER), **65**, 135
 2-AZETIDINONE, 3-METHOXY-1,3-DIMETHYL-4-PHENYL-, **65**, 140
 Azobisisobutyronitrile (AIBN); (78-67-1), **66**, 77, 79, 86; **67**, 86; **69**, 66
 AZOMETHINE YLIDE EQUIVALENT, **67**, 133
 1(2H)-AZULENONE-3,4-DIHYDRO: 1(2H)-AZULENONE, 3,4-DIHYDRO-;
 (52487-41-9), **69**, 180

 Beckmann rearrangement, **66**, 185, 189, 190
 Benzaldehyde; (100-52-7), **65**, 119; **66**, 203; **68**, 83
 Benzaldehyde, 2-bromo-4,5-dimethoxy-, **65**, 108
 Benzaldehyde, 3-nitro-, **67**, 180
 Benzene, (2-bromoethenyl)- (Z)-; (588-73-8), **68**, 130
 Benzene, (1-cyclopenten-1-ylsulfonyl)-, **67**, 157, 163
 Benzene, 2,4-dichloro-1-methoxy-, **67**, 222
 Benzene, 1-(ethynylsulfonyl)-4-methyl-, **67**, 149
 Benzene, 1-methyl-4-(methylthio)-; (623-13-2), **68**, 49
 BENZENE, [(NITROMETHYL)THIO]-; (60595-16-6), **68**, 8
 Benzeneamine, N-hydroxy-, **67**, 187
 Benzeneamine. 2-methyl-3-nitro-, **65**, 146
 1,2-Benzenediol; (120-80-9), **66**, 184; **67**, 98
 Benzenemethanamine, N-(methoxymethyl)-N-[(trimethylsilyl)methyl]-, **67**, 133
 Benzenemethanamine, N-[(trimethylsilyl)methyl]-, **67**, 133
 Benzenemethanaminium, N,N,N-trimethyl-, hydroxide; (100-85-6), **68**, 56
 Benzenemethanol, α -methyl-3-nitro-, **67**, 180

Benzenemethanethiol, **65**, 215

Benzenepropanol, 2-amino-, (S)-; (3182-95-4), **68**, 77

Benzeneseleninic acid, **67**, 157

Benzenesulfonyl chloride; (931-59-9); **68**, 8

Benzenesulfonamide, **66**, 203

Benzenesulfonic acid, hydrazide, **67**, 157

Benzenesulfonoselenic acid, Se-phenyl ester, **67**, 157

1-(BENZENESULFONYL)CYCLOPENTENE: BENZENE, (1-CYCLOPENTEN-1-YLSULFONYL)-; (64740-90-5), **67**, 157, 163

Benzenesulfonyl hydrazide: Benzenesulfonic acid, hydrazide; (80-17-1), **67**, 157

Benzenethiol; (108-98-5), **68**, 8

2H-1-BENZOPYRAN, 3,4-DIHYDRO-2-METHYLENE; (74104-13-5), **69**, 72

2H-1-BENZOPYRAN-3-CARBOXYLIC ACID, 5,6,7,8-TETRAHYDRO-2-OXO-, METHYL ESTER, **65**, 98

p-Benzoquinone; (106-51-4), **67**, 105; **68**, 109; **69**, 38

4H-1,3-BENZOXATHIIN, HEXAHYDRO-4,4,7-TRIMETHYL-, **65**, 215

Benzoyl chloride; (98-88-4), **69**, 45

Benzoyl chloride, 4-nitro-, **67**, 86

1-(2-Benzoylpropanoyl)piperidine: Piperidine, 1-(2-methyl-1,3-dioxo-3-phenylpropyl)-, (±)-; (99114-34-8), **69**, 44

Benzyl alcohol, α-methyl-m-nitro-, **67**, 100

Benzylamine; (100-46-9), **67**, 105, 133; **68**, 227

Benzylamine hydrochloride; (3287-99-8), **68**, 206

N-BENZYL-2-AZANORBORNENE: 2-Azabicyclo[2.2.1]hept-5-ene, 2-(phenylmethyl)-, **68**, 206

Benzyl bromide; (100-39-0), **68**, 92; **69**, 83

Benzylchlorobis(triphenylphosphine)-, trans-: Palladium, benzylchlorobis-(triphenylphosphine)-, trans-; Palladium, chloro(phenylmethyl)bis(triphenylphosphino) , (SP-4 3) ; (22784-60-4), **67**, 86

(±)-Benzyl 2,3-epoxypropyl ether: Oxirane, [(phenylmethoxy)methyl]-; (2930-05-4), **69**, 81, 83

(S)-Benzyl 2,3-epoxypropyl ether: Propane, 1-(benzyloxy)-2,3-epoxy-, (S) ; (14618-80-5), **69**, 83

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride; (4568-71-2), **65**, 26

N-Benzylidenebenzenesulfonamide; (13909-34-7), **66**, 203, 204, 206, 210

Benzylidenemalononitrile: Malononitrile, benzylidene-; Propanedinitrile, (phenylmethylene)-; (2700-22-3), **65**, 32

Benzyl mercaptan: α-Toluenethiol; Benzenemethanethiol; (100-53-8), **65**, 215

N-BENZYL-N-METHOXYMETHYL-N-(TRIMETHYLSILYL)METHYLAMINE: BENZENEMETHANAMINE, N-(METHOXYMETHYL)-N-[(TRIMETHYLSILYL)METHYL]-; (93102-05-7), **67**, 133

1-BENZYLOXY-4-PENTEN-2-OL: 4-PENTEN-2-OL, 1-(PHENYLMETHOXY)-; (58931-16-11), **69**, 80

Benzyltriethylammonium chloride, (56-37-1), **66**, 204; **68**, 220

N-Benzyl-N-(trimethylsilyl)methylamine: Benzenemethanamine, N-[(trimethylsilyl)methyl]-; (53215-95-5), **67**, 133

BETA-LACTAM, **65**, 135, 140

BIARYL SYNTHESIS. **66**, 67

Biaryls, preparation by Pd-catalyzed aryl-aryl coupling, **66**, 73

Bicyclo[2.2.1]hepta-2,5-diene-1,4-bis(diphenylphosphino)butanerhodium trifluoromethanesulfonate, **68**, 64

Bicyclo[2.2.1]hepta-2,5-diene-2,4-pentanedionatorrhodium; (32354-50-0), **68**, 64

BICYCLO[3.1.1]HEPTANE, 6,6-DIMETHYL-2-METHYLENE-, (1S)-, **65**, 224

Bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl-; (1195-79-5), **68**, 14

Bicyclo[3.1.1]hept-2-ene, 2-(2,2-dibromocyclopropyl)-6,6-dimethyl-, (1R), **68**, 220

Bicyclo[3.1.1]hept-2-ene, 2-ethenyl-6,6-dimethyl-, (1R)-; (30293-06-2), **68**, 220

BICYCLO[3.1.1]HEPT-2-ENE, 2,6,6-TRIMETHYL-, (1S)-, **65**, 224

BICYCLO[4.3.0]NON-1-EN-4-ONE: 5H-INDEN-5-ONE, 1,2,3,3a,4,6-
HEXAHYDRO-, **67**, 163

BICYCLO[4.2.0]OCTANE-7-CARBONITRILE, 7-CHLORO-8-OXO, (1 α ,6 α ,7 β)-;
(89937-15-5), **69**, 205

Bicyclo[3.3.0]octane-2,6-diol; (17572-86-0), **68**, 175

BICYCLO[3.3.0]OCTANE-2,6-DIONE: 1,4-Pentalenedione, hexahydro-; (17572-87-1),
68, 175

Bicyclo[2.2.2]octan-2-ones, preparation, **66**, 37, 40

BINAP, (R)-(+)- and (S)-(-)-, **67**, 20, 33

1,1'-Binaphthalene, 2,2'-dibromo-, **67**, 20

1,1'-BINAPHTHALENE-2,2'-DIOL, (R)-(+)-: [1,1'-BINAPHTHALENE]-2,2'-DIOL,
(R)-; (18531-94-7), **67**, 13

Binaphthol, (\pm)-; (41024-90-2), (602-09-5), **67**, 1, 13, 20

Binaphthol, R-(+)-; (18531-94-7); S-(-)-; (1853-99-2), **67**, 13

1,1' BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE, (R)-(-)-: R(-) DI-
NAPHTHO[2,1-d:1'2'-f][1,3,2]DIOXAPHOSPHEPIN, 4-HYDROXY-4-
OXIDE; (39648-67-4), **67**, 1, 13

1,1'-BINAPHTHYL-2,2'-DIYL HYDROGEN PHOSPHATE, (S)-(+)-: S(+) DI-
NAPHTHO[2,1-d:1'2'-f][1,3,2]DIOXAPHOSPHEPIN, 4-HYDROXY-4-
OXIDE; (35193-64-7), **67**, 1

BINAPO, (R)-(+)-, and (S)-(-)-, **67**, 20

[1,1'-BIPHENYL]-2,2'-DICARBOXALDEHYDE, 4,4',5,5'-TETRAMETHOXY-, **65**, 108

Biphenyl, 2-methyl-4'-nitro-; (33350-73-1), **66**, 74

- 1,2-Bis(2-chloroethoxy)ethane: Ethane, 1,2-bis(2-chloroethoxy)-; (112-26-5), **68**, 227
- Bis(cyclopentadienyl)titanium dichloride: Titanium, dichloro- π -cyclopentadienyl-; (1271-19-8), **69**, 72
- [2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL (BINAP). (R)-(+)- and (S)-(-)-: PHOSPHINE, [1,1'-BINAPHTHALENE]-2,2'-DIYLBIS-[DIPHENYL-, (R)- and (S)-]; (R)-: (76189-55-4), (S)-; (76189-56-5), **67**, 20, 33
- 1,4-Bis(diphenylphosphino)butane; (7688-25-7), **68**, 64
- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl-(η^4 -1,5-cyclooctadiene)-rhodium(I) perchlorate. (+)- and (-): Rhodium(1+), [[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine]-P,P'][(1,2,5,6- η)-1,5-cyclooctadiene]-, stereoisomer perchlorate; (+)-; (82822-45-5); (-)-; (82889-98-3), **67**, 33
- 2,2'-Bis(diphenylphosphinyl)-1,1'-binaphthyl, (\pm)-, (S)-(-)-, and (R)-(+)- [(\pm)-, (S)-(-)-, and (R)-(+)-BINAPO]: Phosphine oxide, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (\pm)-, (S)-, and (R)-]; (\pm)-; (866632-33-9); (S)-; (94041-18-6); (R)-; (94041-16-4), **67**, 20
- 1,2-Bis(2-iodoethoxy)ethane: Ethane, 1,2-bis(2-iodoethoxy)-; (36839-55-1), **68**, 227
- N¹N²Bis(methoxycarbonyl)sulfur diimide: Sulfur diimide, dicarboxy-, dimethyl ester; (16762-82-6), **65**, 159
- 1,2-Bis(tributylstannyl)ethylene, (E)-: Stannane, vinylenebis[tributyl-, (E)-; Stannane, 1,2-ethenediylbis[dibutyl-, (E)-; (14275-61-7), **67**, 86
- Bis(tributyltin) oxide: Distannoxane, hexabutyl-; (56-35-9), **68**, 104
- 1,2-Bis(trimethylsiloxy)cyclobut-1-ene: Silane, (1-cyclobuten-1,2-vylenedioxy)bis(trimethyl-: Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl-; (17082-61-0), **65**, 17

1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE: 2,7-DISILAOctA-3,5-DIYNE,
2,2,7,7-TETRAMETHYL-; SILANE, 1,3-BUTADIYNE-1,4-DIYLBIS-
[TRIMETHYL-; (4526-07-2), **65**, 52

BNP acid, R(-) : R(-) Dinaphtho[2,1-d:1'2'-f][1,3,2]dioxaphosphopin,
4-hydroxy-4-oxide, **67**, 1
Compound with 8 α , 9-cinchonan-9-ol; (40481-36-5), **67**, 1

BNP acid, S(+) : S(+) Dinaphtho[2,1-d:1'2'-f][1,3,2]dioxaphosphopin,
4-hydroxy-4-oxide, **67**, 1
Compound with 9S-cinchonan-9-ol; (3974950-3), **67**, 1

Borane-dimethylsulfide; (13292-87-0), **68**, 77

Borane, tetrahydrofuran complex, **69**, 214

Borate(1-), tetrafluoro-, hydrogen, compound with oxybis[methane], **67**, 141

Boric acid, **69**, 169

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃) (1:1);
Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1); (109-63-7), **65**, 171;
67, 52, 205; **68**, 77

Bromine, **69**, 10

Bromobenzene; (108-86-1), **69**, 2

4-Bromobutanenitrile: Butyronitrile, 4-bromo-; Butanenitrile, 4-bromo-;
(5332-06-9), **67**, 193

2-Bromo-2-butene (cis and trans mixture): 2-Butene, 2-bromo-; (13294-71-8), **65**, 42

1-Bromo-3-chloro-2,2-dimethoxypropane: 2-Propanone, 1-bromo-3-chloro-,
dimethyl acetal; Propane, 1-bromo-3-chloro-2,2-dimethoxy-; (22089-54-9), **65**, 2

1-Bromo-1-chloromethane, **67**, 76

6-Bromo-3,4-dimethoxybenzaldehyde: Benzaldehyde, 2-bromo-4,5-dimethoxy-;
(5392-10-9), **65**, 108

6-Bromo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine
 N-[(2-bromo-4,5-dimethoxyphenyl)methylene]-; (73252-55-8), **65**, 108

1-BROMO-1-ETHOXYCYCLOPROPANE: CYCLOPROPANE, 1-BROMO-1-
 ETHOXY-; (95631-62-2), **67**, 210

Bromoform; (75-25-2), **68**, 220

1-Bromohexanoate, ethyl: Hexanoic acid, 2-bromo-, ethyl ester, (\pm)-;
 (63927-44-6), **69**, 10

BROMOMETHANESULFONYL BROMIDE; METHANESULFONYL BROMIDE,
 BROMO-; (54730-18-6), **65**, 90

2-(Bromomethyl)-2-(chloromethyl)-1,3-dioxane: 1,3-Dioxane, 2-(bromomethyl)-
 2-(chloromethyl)-; (60935-30-0), **65**, 32

N Bromomethylphthalimide: Phthalimide, N (bromomethyl) ; 1H Isoindolo
 1,3-(2H)-dione, 2-(bromomethyl)-; (5332-26-3), **65**, 119

1-Bromo-4-nitrobenzene, **66**, 68

(Z)- β -Bromostyrene: Styrene, β -bromo-, (Z)-; (588-73-8), **68**, 130

N-BROMOSUCCINIMIDE: SUCCINIMIDE, N-BROMO-; 2,5-PYRROLIDINEDIONE,
 1-BROMO-; (128-08-5), **65**, 243

o Bromotoluene, **66**, 69

Brook rearrangement, **66**, 19

Butadiyne, **65**, 52

BUTANAL, 2-METHYL-, (S)-; (1730-97-8), **69**, 212

Butane, 4-bromo-, 1,1,1-trimethoxy-, **67**, 193

Butane, 1-chloro-, **65**, 61

Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]- and [S-(R*,R*)]-, **67**, 20

Butanedioic acid, bis[5-methyl-2-(1-methylethyl)-cyclohexyl]ester,
 [1R-[1 α (1R*,2S*,5R*), 2 β ,5 α]-, **67**, 76

Butanedioic acid, 2,3-dihydroxy-, [R-(R*,R*)]-; (87-69-4), **68**, 92

Butanedioic acid, 2,3-dihydroxy-, diethylester, [S-(R*,R*)]-; (13811-71-7), **68**, 49
 Butanedioic acid, dioxo-, diethyl ester; (59743-08-7), **66**, 149
 Butanedioic acid, tetrahydroxy-, disodium salt; (866-17-1), **66**, 149
 2,3-Butanediol, 1,4-bis(benzyloxy)-, (2S,3S)-; (17401-06-8), **68**, 92
 2,3-Butanediol, 1,4-bis(phenylmethoxy)-, [S[(R*,R*)]]-; (17401-06-8), **68**, 92
 Butanenitrile, 4-bromo-, **67**, 193
 Butanoic acid, 4-bromo-, ethyl ester, **67**, 98
 Butanoic acid, 4-iodo-, ethyl ester, **67**, 98
 1-Butanol, 2-amino-3-methyl-, (S)-, **67**, 52
 1-Butanone, 3-hydroxy-3-methyl-1-phenyl-, **65**, 6, 12
 2-Butene, 2-bromo-, **65**, 42
 2-Butene, 1-bromo-3-methyl-, (870-63-3), **66**, 85
 2-Butene, 2-methyl-, **65**, 159
 2-Butenoic acid, 2-methyl-, methyl ester, (E); (6622-76-0), **66**, 94
 2-Butenoic acid, 4-(4-nitrophenyl)-4-oxo-, ethyl ester, **67**, 86
 2-Buten-1-ol, 4-chloro-, acetate (E)-, **67**, 105
 3-Buten-1-ol, 2-chloro-, acetate, **67**, 105
 2-Butenol, 4-(diethylamino)-, acetate, **67**, 105
 Butenolide synthesis, from furfural, **68**, 162
 2-Buten-1-one, 3-methyl-1-phenyl-, **65**, 12
 3-Buten-2-one; (78-94-4), **65**, 26
 N-tert-BUTOXYCARBONYL-L-LEUCINAL: CARBAMIC ACID, (1-FORMYL-3-METHYLBUTYL)-, 1,1-DIMETHYLETHYL ESTER, (S)-; (5821-45-2), **67**, 69
 N-tert-Butoxycarbonyl-L-leucine N-methyl-O-methylcarboxamide: Carbamic acid, [1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester, (S)-; (87694-50-6), **67**, 69

N-tert-Butoxy-L-leucine hydrate: Leucine, N-carboxy-, N-tert-butyl ester, L-;

L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-; (13139-15-6), **67**, 69

tert-Butyl alcohol, potassium salt, **67**, 125

tert-BUTYL ACETOTHIOACETATE; (15925-47-0), **66**, 108, 112, 114

Butyl bromide, **66**, 118

p-tert-BUTYLCALIX[4]ARENE: Pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacos-

1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetraol,
5,11,17,23-tetrakis(1,1-dimethylethyl)-; (60705-62-6), **68**, 234

p-tert-BUTYLCALIX[6]ARENE: Heptacyclo[31.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}]-

octetraconta-1(37),3,5,7(42),9,11,13(41),15,17,19,(40),21,23,25(39),-
27,29,31(38),33,35-octadecaene-37,38,39,40,41,42-hexol, 5,11,17,23,29,35-
hexakis (1,1-dimethylethyl)-; (78092-53-2), **68**, 238

p-tert-BUTYLCALIX[8]ARENE: Nonacyclo[43.3.1.1^{3,7}.1^{9,13}.1^{15,19}.1^{21,25}.1^{27,31}.1^{33,37}-

1^{39,43}]hexapentaconta-1(49),3,5,7(56),9,11,13(55),15,17,19(54),21,23,-
24(53),27,29,31(52),33,35,37(51),39,41,43(50),45,47-tetracosae-
49,50,51,52,53,54,55,56-octol, 5,11,17,23,29,35,41,47-octakis(1,1-dimethyl
ethyl)-; (68971-82-4), **68**, 243

3-BUTYLCYCLOBUTENONE: 2-Cyclobuten-1-one, 3-butyl-; (38425-48-8), **68**, 32

4-tert-Butylcyclohexanone: Cyclohexanone, 4-(1,1-dimethylethyl); (98-53-3), **68**, 116

1-(4-tert-BUTYLCYCLOHEXEN-1-YL)-2-PROPEN-1-ONE: 2-Propen-1-one, 1-[4-(1,1-
dimethylethyl)-1-cyclohexen-1-yl]-; (92622-56-5), **68**, 116

4-tert-Butylcyclohexen-1-yl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro,
4-(1,1-dimethylethyl)-1-cyclohexen-1-yl ester; (77412-96-5), **68**, 116

3-Butyl-4,4-dichlorocyclobutenone: 2-Cyclobuten-1-one, 3-butyl-4,4-dichloro-;
(72284-70-9), **68**, 32

tert-Butylhydrazine hydrochloride: Hydrazine, tert-butyl, monohydrochloride;

Hydrazine, (1,1-dimethylethyl)-, monohydrochloride; (7400-27-3), **65**, 166

3-tert-Butyl-4-hydroxy-5-methylphenyl sulfide, **66**, 16

8-n-Butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one: 5,9-Methanobenzocycloocten-11-one, 10-butylidodecahydro-4a-hydroxy-; (24133-22-0), **69**, 227

tert-Butyllithium, **66**, 15, 16, 18, 67, 69; **67**, 60, 210; **68**, 25

Butyllithium: Lithium, butyl-; (109-72-8), **65**, 98, 108, 119;

66, 14, 16, 37, 39, 88, 194, 196; **67**, 44, 48; **68**, 14, 41, 83, 155, 162, 210

69, 44, 56, 114, 121, 175, 188, 220

Butylmagnesium bromide, **66**, 116, 118

Butyl methyl ether, **69**, 33, 6

9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine: Acridine, 9-butyl-1,2,3,4,5,6,7,8-octahydro-; (99922-90-4), **69**, 227

9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide, **69**, 228

9-N-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL: 4-ACRIDINOL. 9-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDRO-; (99922-91-5), **69**, 226

N-tert-Butyl-N-tert-octyl-O-tert-butylhydroxylamine: 2-Pentanamine, N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-2,4,4-trimethyl-; (90545-93-0), **65**, 166

TERT-BUTYL-TERT-OCTYLAMINE; 2-PENTANAMINE, N-(1,1-DIMETHYLETHYL)-2,4,4-TRIMETHYL-; (90545-94-1), **65**, 166

S-tert-Butyl 3-oxobutanethioate, **66**, 108, 109

p-tert-Butylphenol: Phenol, p-tert-butyl-; (98-54-4), **68**, 234, 238, 243

4-tert-BUTYL-1-VINYLCYCLOHEXENE: Cyclohexene, 4-tert-butyl-1-vinyl-; (33800-81-6), **68**, 116

2-Butynedioic acid, dimethyl ester; (762-42-5), **68**, 198

2-BUTYNOIC ACID, 4-CHLORO-, METHYL ESTER, **65**, 47

3-Butyn-1-ol; (927-74-2), **68**, 182

3-Butyn-2-ol; (65337-13-5), **67**, 141

- (+)-(1S)-10-Camphorsulfonamide: Bicyclo[2.2.1]heptane-1-methanesulfonamide, 7,7-dimethyl-2-oxo- (1S)-; (60933-63-3), **69**, 158
- (1S)-(+)-10-Camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1S)-; (3144-16-9), **69**, 160
- (+)-10-Camphorsulfonyl chloride: Bicyclo[2.2.1]heptane-1-methanesulfonyl chloride, 7,7-dimethyl-2-oxo-, (+)-; (21286-54-4), **69**, 159
- (-)-(Camphorsulfonyl)imine: 3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-, 2,2-dioxide, (3aS)-; (60886-80-8), **69**, 154, 159
- (+)-(2R,8aS)-10-(CAMPHORSULFONYL)OXAZIRIDINE: 4H-4a,7-METHANO-OXAZIRINO-[3,2-i][2,1]BENZISOTHIAZOLE, TETRAHYDRO-9,9-DIMETHYL-3,3-DIOXIDE, [4aS-(4a α ,7 α ,8aR*)]-; (104322-63-6), **69**, 158, 159
- (-)-D-2,10-CAMPHORSULTAM: 3H-3a,6-METHANO-2,1-BENZISOTHIAZOLE, HEXAHYDRO-8,8-DIMETHYL-, 2,2-DIOXIDE, [3aS-(3a α ,6 α ,7a β)]-; (94594-90-8), **69**, 154
- Carbamic acid, dichloro-, methyl ester, **65**, 159
- Carbamic acid, (1-formyl-3-methylbutyl)-, 1,1-dimethylethyl ester, (S)-, **67**, 69
- Carbamic acid, [1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester, (S)-, **67**, 69
- CARBAMIC ACID, (2-METHYL-2-BUTENYL)-, METHYL ESTER, **65**, 159
- Carbamic acid, methyl ester, **65**, 159
- Carboalumination of alkynes, **66**, 64
- Carbocupration of alkynes, **66**, 65
- 1-Carbomethoxy-1-methylethyl-3-oxobutanoate, **66**, 110
- 2-CARBOMETHOXY-3-VINYLCYCLOPENTANONE; (75351-19-8), **66**, 52, 53, 56, 59
- Carbonic acid, dicesium salt, **65**, 150
- Carbon monoxide; (630-08-0), **68**, 109; **69**, 114
- Carbonochloridic acid, methyl ester, **65**, 47

Carbonylative coupling reaction, **68**, 116
 3-Carboxy-5-dodecen-2-one, (E), **68**, 210
 Carboxylation, vicinal di-, **68**, 41
 Carboxylic acids, reduction, **66**, 160
 (E)-(Carboxyvinyl)trimethylammonium betaine; (54299-83-1), **66**, 29, 30, 33, 36
 Carroll rearrangement, **68**, 210
 (R)-(-)-Carvone; (6485-40-1), **66**, 8, 9, 13
 CATALYTIC TRANSFER HYDROGENATION, **67**, 187
 Catechol, **66**, 180, 182
 Catecholborane: 1,3,2-Benzodioxaborole; (274-07-7), **68**, 130
 Cellulose chromatography, **66**, 213, 216
 Cerate(2-), hexanitrate-, diammonium, **67**, 141
 Ceric ammonium nitrate: Cerate(2-), hexanitrate-, diammonium; Cerate(2-),
 hexakis(nitrate-0)-, diammonium, (OC-6-11); (16774-21-3), **67**, 141
 Cerium(III) chloride, heptahydrate; (18618-55-8), **69**, 89
 Cesium carbonate: Carbonic acid, dicesium salt; (534-17-8), **65**, 150
 CESIUM THIOLATES, **65**, 150
 Chiral auxiliary, **65**, 173, 183, 203, 215
 Chiral oxazolidinone auxiliary, from phenylalanine, **68**, 77, 83
 Chirasil-Val, **66**, 153, 154
 CHLORINATION OF ELECTRON-RICH BENZENOID COMPOUNDS, **67**, 222
 Chloroacetaldehyde diethyl acetal; (621-62-5), **66**, 96, 100, 107
 Chloroacetyl chloride: Acetyl chloride, chloro-; (79-04-9), **69**, 2
 (S)-2-Chloroalkanoic acids
 determination of enantiomeric purity, **66**, 154
 properties, **66**, 155
 (S)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY, **66**, 151

(S)-2-CHLOROALKANOIC ACIDS VIA (S)-2-CHLORO-1-ALKANOLS, **66**, 160

(S)-2-Chloroalkan-1-ols, properties, **66**, 168

N-Chloroamines, **67**, 222

1-Chlorobutane: Butane, 1-chloro-; (109-69-3), **65**, 61

7-CHLORO-7-CYANOBICYCLO[4.2.0]OCTAN-8-ONE: BICYCLO[4.2.0]OCTANE-7-CARBONITRILE, 7-CHLORO-8-OXO-, (1 α ,6 α ,7 β)-; (89937-15-5), **69**, 205

Chlorocyanoketene, **69**, 205

2-CHLORO-2-CYCLOPROPYLIDENACETIC ACID, METHYL ESTER: ACETIC ACID, CHLOROCYCLOPROPYLIDENE METHYL ESTER; (82979-15-1) **69**, 148

(Chlorodimethylsilyl)methyl chloride, **69**, 98

α -Chloroenamines, **66**, 119

2-Chloroethanol; Ethanol, 2-chloro-; (107-07-3), **65**, 150

2-Chloroethyl dichlorophosphate: Phosphorodichloridic acid, 2-chloroethyl ester; (1455-05-6), **65**, 68

Chlorohydrins, preparation from α -chloro acids, **66**, 161

2-Chloromethoxybenzene: Anisole, o-chloro-; Benzene, 1-chloro-2-methoxy-; (766-51-8), **67**, 222

(S)-2-Chloro-3-methylbutan-1-ol, **66**, 164

6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one; (81956-31-2), **66**, 194, 195, 202
(2S,3S)-2-Chloro-3-methylpentanoic acid, **66**, 154

(2S,3S)-2-Chloro-3-methylpentan-1-ol, **66**, 164

(S)-2-Chloro-4-methylpentan-1-ol, **66**, 164

Chloromethyltrimethylsilane: Silane, (chloromethyl)trimethyl-; (2344-80-1); **67**, 133;
68, 1, 182

N-Chloromorpholine: Morpholine, 4-chloro-; (23328-69-0), **67**, 222

m-Chloroperoxybenzoic acid, **66**, 204; **69**, 231

1-Chloro-4-phenyl-2-butanone; (10290-42-3), **69**, 183

(S)-2-CHLOROPROPANOIC ACID; (29617-66-1), **66**, 151, 154, 159, 160, 172

(S)-2-Chloropropan-1-ol; (19210-21-0), **66**, 160, 164, 172

N-Chlorosuccinimide; (128-09-6), **66**, 211, 214, 219

Chlorosulfonyl isocyanate: Sulfuryl chloride isocyanate; (1189-71-5), **65**, 135

Chlorotetrolic ester, **65**, 47

1-Chloro-1-(trichloroethenyl)cyclopropane: Cyclopropane, 1-chloro-1-(trichloroethenyl)-; (82979-27-9), **69**, 144, 148

1-Chloro-N,N,2-trimethylpropenylamine; (26189-59-3), **66**, 116, 117, 119, 120

Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4), **65**, 1, 6, 61;
66, 14, 16, 21, 44; **68**, 25
as catalyst for conjugate addition, **66**, 47

1-Chloro-3-trimethylsilylpropane; (2344-83-4), **66**, 88, 90, 94

CHOLESTA-3,5-DIENE; (747-90-0), **68**, 138

Cholesta-3,5-dienyl trifluoromethanesulfonate: Cholesta-3,5-dien-3-ol, trifluoromethanesulfonate; (95667-40-6), **68**, 138

Cholest-4-en-3-one; (601-57-0), **68**, 138

Chromium carbonyl, **65**, 140

Chromium hexacarbonyl: Chromium carbonyl (OC-6-11); (13007-92-6), **65**, 140

Chromium pentacarbonyl (1-methoxyethylidene)-. **65**, 140

Cinchonidine: 8 α , 9R-Cinchonan-9-ol; (485-71-2), **67**, 1

Cinchonine: 9S-Cinchonan-9-ol; (119-10-5), **67**, 1

Cinnamyl alcohol; (104-54-1), **66**, 30, 32, 36

(RS)-Citronellal, **69**, 32

(S)-Citronellal, **69**, 33

CITRONELLAL, (R)-(+)-: 6-OCTENAL, 3,7-DIMETHYL, (R)-(+)-; (2385-77-5),
67, 33; **69**, 3

(S)-Citronellol, **69**, 34

Claisen rearrangement, of propargyl alcohols, **66**, 22

Cobalt(1+), hexacarbonyl[$\mu[(2,3-\eta:2,3-\eta)-1\text{-methyl-2-propynyl}]$]₂-, tetrafluoroborate(1⁻), **67**, 141

Cobalt, octacarbonyl-, **67**, 141

2,4,6-Collidine: Pyridine, 2,4,6-trimethyl-; (108-75-8), **69**, 199

CONJUGATE ADDITION/CYCLIZATION OF A CYANOCUPRATE, **66**, 52

CONJUGATE ADDITION, ZINC HOMOENOLATES TO ENONES, **66**, 43, 50

CONJUGATED DIENES, SYNTHESIS OF, **66**, 60, 64

Copper(II) acetate monohydrate; (6046-93-1), **69**, 228

Copper(I) bromide (7787-70-4), **65**, 203; **66**, 2, 3, 44, 45

Copper, bromo[thiobis(methane)]-; (54678-23-8), **66**, 51

Copper chloride (CuCl); (7758-89-6), **66**, 180, 182, 184; **67**, 121; **69**, 2

Copper(I) chloride - tetramethylethylenediamine complex, **65**, 52

Copper, compound with zinc (1:1), **67**, 98

Copper cyanide (CuCN), **66**, 53, 55; **69**, 80

Copper iodide (CuI), **66**, 97, 100, 116, 118

Crotonaldehyde; (123-73-9), **67**, 210

Cumene hydroperoxide: Hydroperoxide, α,α -dimethylbenzyl; hydroperoxide, 1-methyl-1-phenylethyl; (80-15-9), **68**, 49

Cuprate addition, **66**, 52, 95

Cuprate, dibutyl-, lithium, reaction with acetylene, **66**, 62

Cuprates, higher order, **66**, 57

Cuprous bromide/dimethyl sulfide; (54678-23-8), **66**, 51; **68**, 198

Cuprous chloride-pyridine complex, **66**, 182

[2 + 2] CYCLOADDITION, **65**, 135; **68**, 32

Cyclobutanecarboxamide; (1503-98-6), **66**, 132, 134, 136, 141

Cyclobutanecarboxylic acid; (3721-95-7), **66**, 133, 135, 141

Cyclobutanone, 2-(1-propenyl)-, (E)-, **67**, 210

CYCLOBUTANONES, **67**, 210

2-Cyclobuten-1-one, 3-butyl-; (38425-48-8), **68**, 32

CYCLOBUTYLAMINE, **66**, 132

Cyclobutylamine hydrochloride; (6291-01-6), **66**, 134, 135, 141

Cycloheptene; (628-92-2), **68**, 109

2-CYCLOHEPTEN-1-YL ACETATE: 2-Cycloheptene-1-ol, acetate;
(628-92-2), **68**, 109

1,3-Cyclohexadiene; (592-57-4), **68**, 148; **69**, 38

Cyclohexanamine, **65**, 108

Cyclohexanamine, N-[(2-bromo-4,5-dimethoxyphenyl)methylene]-, **65**, 108

Cyclohexanamine, N-[(2-iodo-4,5-dimethoxyphenyl)methylene]-, **65**, 108

CYCLOHEXANE, 1,2-BIS(METHYLENE)-, **65**, 90

Cyclohexane, 1,1-diethoxy-, **65**, 17

CYCLOHEXANE, 1,2-DIMETHYLENE, **65**, 90

1,3-CYCLOHEXANEDIOL, 2-NITRO, 1-ACETATE, [1S-(1 α ,2 β ,3 α)];
(108186-61-4), **69**, 19

CYCLOHEXANE, 5-METHYL-1-METHYLENE-2-(1'-METHYLETHYL)-, R,R-, **65**, 81

CYCLOHEXANEBUTANOIC ACID, γ -OXO-, ETHYL ESTER, **65**, 17

CYCLOHEXANEMETHANOL, 1-HYDROXY-; (15753-47-6), **69**, 96

Cyclohexanol, 2-(1-mercapto-1-methylethyl)-5-methyl-, [(1R-(1 α ,2 α ,5 α))], **65**, 215

Cyclohexanol, 5-methyl-2-(1-methylethyl)-: (-)-Menthol, [1R-(1 α ,2 β ,5 α)]-, (2216-51-5),
67, 76; **68**, 155

Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2 β ,5 β)], **65**, 81

CYCLOHEXANOL, 5-METHYL-2-(1-METHYL-1-PHENYLETHYL)-, [1R-(1 α ,2 β ,5 α)]-,
65, 203

Cyclohexanol, 2-phenyl-, trans-(\pm)-; (40960-69-8), **69**, 2

CYCLOHEXANOL, 2-PHENYL, (1R-trans); (98919-68-7), **69**, 1
 CYCLOHEXANOL, 2-PHENYL, (1S-trans); (34281-92-0), **69**, 1
 Cyclohexanone; (108-94-1), **65**, 98; **67**, 141; **69**, 97, 227
 Cyclohexanone diethyl ketal; Cyclohexane, 1,1-diethoxy-; (1670-47-9), **65**, 17
 Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)-, **65**, 81
 CYCLOHEXANONE, 5-METHYL-2-(1-METHYLETHYLIDENE)-, (R)-, **65**, 203, 215
 Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)-, **65**, 203
 Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)-, **65**, 203
 Cyclohexanone, 5-methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]-,
 (2R-trans)-; (79563-58-9); (2S-cis)-; (79618-04-5), **65**, 215
 Cyclohexanone oxime, (100-64-1), **65**, 185, 187, 193
 Cyclohexanone oxime methanesulfonate; (80053-69-6), **66**, 185, 186, 193
 Cyclohexene, **69**, 206
 1-Cyclohexene-1-carboxaldehyde, 3-hydroxy-, **67**, 205
 Cyclohexene, 4-(1,1-dimethylethyl)-1-ethenyl-; (33800-81-6), **68**, 116
 1-Cyclohexene-1-methanol, 4-(1-methylethenyl)-, **67**, 176
 1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)-, **67**, 176
 Cyclohexene, 1-methyl-, **65**, 90
 Cyclohexene oxide: 7-Oxabicyclo[4.1.0]heptane: (286-20-4). **69**, 2
 2-Cyclohexene-1-propanoic acid, 3-[(trimethylsilyl)oxy]-,
 ethyl ester; (90147-64-1), **66**, 51
 2-Cyclohexen-1-ol, 1-(1,3-dithian-2-yl)-, **67**, 205
 2-Cyclohexen-1-one; (930-68-7), **66**, 44, 45, 51, 95, 97, 101, 107; **67**, 205; **69**, 189
 Cyclohexylamine; Cyclohexanamine; (108-91-8), **65**, 108
 cis,cis-1,5-Cyclooctadiene: 1,5-Cyclooctadiene, (Z,Z)-; (1552-12-1), **68**, 175
 Cyclopentadiene; (542-92-7), **68**, 198; 206
 Cyclopentadiene, annulation from 1,3-diene, **68**, 220

1,3-CYCLOPENTADIENE, 1,2,3,4,5-PENTAMETHYL-, **65**, 42

Cyclopentadienes, synthesis, **66**, 11

Cyclopentadiene monoepoxide: 6-Oxabicyclo[3.1.0]hex-2-ene; (7129-41-1),
67, 114

1,2-Cyclopentanedicarboxylic acid, 1-methyl-, cis-(±)-; (70433-31-7), **68**, 41

Cyclopentanes, synthesis, **66**, 10

CYCLOPENTANONE SYNTHESIS, **66**, 87, 92, 93

Cyclopentanone, 2-carbomethoxy-3-vinyl, **66**, 56

Cyclopentanone, 2-ethenyl-2-methyl; (88729-76-4), **66**, 94

Cyclopentene; (142-29-0), **67**, 157

4-Cyclopentene-1,3-diol, monoacetate, cis-, **67**, 114

2-Cyclopenten-1-one, 4,4-dimethyl-, **67**, 121, 205

2-CYCLOPENTEN-1-ONE, 3-METHYL-2-PENTYL-, **65**, 26

CYCLOPROPANATION, **67**, 176

with dibromocarbene, **68**, 220

Cyclopropane, 1-bromo-1-ethoxy-, **67**, 210

Cyclopropane, 1-chloro-1-(trichloroethenyl)-; (82979-27-9), **69**, 144

CYCLOPROPANE -1,2-DICARBOXYLIC ACID, (+)-(1S,2S)-: 1,2-CYCLOPRO-
PANEDICARBOXYLIC ACID, (S,S)-(+)-; 1,2-CYCLOPROPANEDI-
CARBOXYLIC ACID, (1S-trans)-; (14590-54-6) **67**, 76

1,2-Cyclopropanedicarboxylic acid, (S,S)-(+)-, **67**, 76

1,2-Cyclopropanedicarboxylic acid, bis[5-methyl-2-(1-methylethyl)cyclohexyl]
ester, **67**, 76

Cyclopropane, 1-trimethylsiloxy-1-ethoxy-, **66**, 44

Cyclopropanecarboxylic acid chloride, **66**, 176

CYCLOPROPENONE 1,3-PROPANEDIOL KETAL: 4,8-DIOXASPIRO[2.5]OCT-1-ENE;
(60935-21-9), **65**, 32

Cyclopropylpropionic acid ethyl ester, **66**, 177

Davis reagent, **66**, 203

Decanoic acid, ethyl ester, **67**, 125

Decanoic acid, 2-(methyldiphenylsilyl)-, ethyl ester, **67**, 125

Decanoic acid, 6-oxo-; (4144-60-9), **66**, 126

Decanoic acid, 6-oxo-, methyl ester; (61820-00-6), **66**, 120

Decarboxylation, of β -keto acid, **68**, 210

(E)-1-Decenyldiisobutylalane, **66**, 60, 61

Dechlorination, reductive, **68**, 32

1-Decyne; (764-93-2), **66**, 60, 61, 66

2-DECYN-1-OL; (4117-14-0), **66**, 127, 128, 131

9-DECYN-1-OL; (17643-36-6), **66**, 127, 128, 131

1-DEOXY-2,3,4,6-TETRA-O-ACETYL-1-(2-CYANOETHYL)- α -D-GLUCOPYRANOSE:

D-GLYCERO-D-IDO-NONONONITRILE, 4,8-ANHYDRO-2,3-DIDEOXY-,

5,6,7,9-TETRAACETATE; (86563-27-1), **65**, 236

2,6-Diacetoxycyclo[3.3.0]octane: 1,4-Pentalenediol, octahydro-, diacetate;

(17572-85-9), **68**, 175

(1,1-Diacetoxiodo)benzene, **66**, 136

DIALKOXYACETYLENES, **65**, 68

1,3-Diaminopropane; (109-76-2), **66**, 127, 128, 131

1,4-Diazabicyclo[2.2.2]octane; (280-57-9), **68**, 64

4,13-DIAZA-18-CROWN-6: 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane;

(23978-55-4), **68**, 227

Diazomethane: Methane, diazo-; (334-88-3), **69**, 180, 182

Diazomethane substitute; trimethylsilyldiazomethane, **68**, 1

1-Diazo-4-phenyl-2-butanone: 2-Butanone, 1-diazo-4-phenyl-; (10290-42-3), **69**, 180

Diazotization of amino acids. **66**. 151. 156

2,3-O-Dibenzoyl-L-tartaric acid monohydrate, (-)- and (+)- [(-)-DBT and (+)-DBT monohydrate]: Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]- and [S-(R*,R*)]-: [R-(R*,R*)]-; (2743-38-6); [S-(R*,R*)]-; (17026-42-5)
67, 20

1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane: Benzenemethanamine, N,N'-[1,2-ethanediylbis(oxy-2,1-ethanediyl)]bis-; (66582-26-1), **68**, 227

1,4-DI-O-BENZYL-L-THREITOL: 2,3-Butanediol, 1,4-bis(phenylmethoxy)- [S-(R*,R*)]-; (17401-06-8), **68**, 92

2,2'-Dibromo-1,1'-binaphthyl: 1,1'-Binaphthalene, 2,2'-dibromo-; (74866-28-7),
67, 20

Dibromocarbene; **68**, 220

Dibromomethane: Methane, dibromo-; (74-95-3), **65**, 81

1,2-Di-tert-butoxy-1-chloroethene, (E)-: Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E); (70525-93-8), **65**, 58

1,2-Di-tert-butoxy-1,2-dichloroethane, dl-: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediyl)]bis(oxy)bis[2-methyl-, (R*,R*)-(±)-; (68470-80-4), **65**, 68

1,2-Di-tert-butoxy-1,2-dichloroethane, meso-: Propane, 2,2'-[(1,2-dichloro-1,2-ethanediyl)bis(oxy)]bis[2-methyl-, (R*,S*)-; (68470-81-5), **65**, 68

2,3-Di-tert-butoxy-1,4-dioxane, cis-: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis-; (68470-78-0), **65**, 68

2,3-Di-tert-butoxy-1,4-dioxane, trans-: 1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans-; (68470-79-1), **65**, 68

DI-TERT-BUTOXYETHYNE; PROPANE, 2,2'-[1,2-ETHYNEDIYLBIS(OXY)]BIS[2-METHYL-; (66478-63-5), **65**, 68

Dibutylboron triflate: Methanesulfonic acid, trifluoro-, anhydride with dibutylborinic acid; (60669-69-4), **68**, 83

- 2,6-Di-tert-butyl-4-methylpyridine: Pyridine, 2,6-bis(1,1-dimethylethyl)-4-methyl;
(38222-83-2), **68**, 116, 138
- Dicarbonyl(cyclopentadienyl)diron, [(CO)₂CpFe]₂; (12154-95-9),
66, 96, 99, 106
- Dicarbonyl(cyclopentadienyl)(ethyl vinyl ether)iron tetrafluoroborate,
66, 96, 106
- Dicarbonyl(cyclopentadienyl)(trans-3-methyl-2-vinylcyclohexanone)iron
tetrafluoroborate, **66**, 97
- Di-μ-chlorobis(η⁴-1,5-cyclooctadiene)dirhodium(I). Rhodium, di-μ-chlorobis-
[(1,2,5,6-η)-1,5-cyclooctadiene]di-; (12092-47-6), **67**, 33
- Dichlorobis(triphenylphosphine)palladium(II): Palladium,
dichlorobis(triphenylphosphine)-; (13965-03-2), **68**, 130
- 2,3-Dichloro-1,4-dioxane, trans-: 1,4-Dioxane, 2,3-dichloro-, trans-;
(3883-43-0), **65**, 68
- 1,2-Dichloroethane, **69**, 199
- (1,1-Dichloroiodo)benzene, **66**, 137
- 3,4-Dichloro-5-isopropoxy-2(5H)-furanone: 2(5H)-Furanone, 3,4-dichloro-5-
(1-methylethoxy)-; (29814-12-8), **69**, 205, 206
- Dichloroketene, **68**, 32
- 2,4-DICHLOROMETHOXYBENZENE: ANISOLE, 2,4-DICHLORO-; BENZENE,
2,4-DICHLORO-1-METHOXY-; (553-82-2), **67**, 222
- 7,7-Dichloro-1-methylbicyclo[3.2.0]heptan-6-one: Bicyclo[3.2.0]heptan-6-one,
7,7-dichloro-1-methyl-; (51284-43-6), **68**, 41
- Dicobalt octacarbonyl: Cobalt, octacarbonyldi-, (Co-Co); (15226-74-1), **67**, 141
- 5,5-Dicyano-4-phenylcyclopent-2-enone 1,3-propanediol ketal:
6,10-Dioxaspiro[4,5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-;
(88442-12-0), **65**, 32

Dicyclopentadiene, **66**, 99

Dieckmann cyclization, **66**, 52

DIELS-ALDER REACTION:

domino, **68**, 198

immonium ion-based, **68**, 206

INVERSE ELECTRON DEMAND, **66**, 142, 147, 148

of triethyl 1,2,4-triazine-3,5,6-tricarboxylate, **66**, 150

Diels-Alder reactions, **66**, 40

1,3-Dione synthesis, via palladium-catalyzed coupling, **68**, 116, 130

5,6-Diethoxybenzofuran-4,7-dione, **69**, 220

3,4-Diethoxy-3-cyclobutene-1,2-dione: 3-Cyclobutene-1,2-dione,

3,4-diethoxy-; (5231-87-8), **69**, 221, 222

Diethylamine, **66**, 145; **67**, 44, 48, 105

Diethyl aminomethylphosphonate: Phosphonic acid, (aminomethyl)-,

diethyl ester; (50917-72-1), **65**, 119

Diethylaminosulfur trifluoride: Sulfur, (diethylamino)trifluoro-; (38078-09-0), **69**, 49

Diethylamino(trimethyl)silane: Silanamine, N,N-diethyl-1,1,1-trimethyl-;

(996-50-9), **69**, 49

DIETHYL N-BENZYLIDENEAMINOMETHYLPHOSPHONATE: PHOSPHONIC ACID,

[[[(PHENYLMETHYLENE)AMINO]METHYL]-, DIETHYL ESTER;

(50917-73-2), **65**, 119

Diethyl carbonate; (105-58-8), **68**, 77

Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate, **66**, 173, 174

N,N-DIETHYL-(E)-CITRONELLAENAMINE, (R)-(-)-: 1,6-OCTADIEN-1-AMINE,

N,N-DIETHYL-3,7-DIMETHYL-, [R-(E)]-; (67392-56-7), **67**, 33

Diethyl cyclopropylcarbonylmalonate; (7394-16-3), **66**, 175, 179

Diethyl cyclopropylmalonate, **66**, 173

Diethyl dioxosuccinate: (59743-08-7), **66**, 144, 149

N,N-DIETHYLGERANYLAMINE; 2,6-OCTADIEN-1-AMINE, N,N-DIETHYL-3,7-DIMETHYL-, (E)-; (40267-53-6), **67**, 33, 44

Diethyl isocyanomethylphosphonate: Phosphonic acid, (isocyanomethyl)-, diethyl ester; (41003-94-5), **65**, 119

Diethyl malonate; (105-53-3), **66**, 175, 179; **69**, 174

N,N-DIETHYLNERYLAMINE: 2,6-OCTADIEN-1-AMINE, N,N-DIETHYL-3,7-DIMETHYL-, (Z)-; (40137-00-6), **67**, 33, 48

Diethyl oxalate: Oxalic acid, diethyl ester; Ethanedioic acid, diethyl ester; (95-92-1). **65**. 146

Diethyl phosphite; (762-04-9), **66**, 195, 197, 202

6-DIETHYLPHOSPHONOMETHYL-2,2-DIMETHYL-1,3-DIOXEN-4-ONE, **66**. 194-196. 202

Diethyl phthalimidomethylphosphonate: Phosphonic acid, (phthalimidomethyl)-, diethyl ester; Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-methyl]-, diethyl ester; (33512-26-4). **65**, 119

Diethyl squarate: 3-Cyclobutene-1,2-dione, 3,4-diethoxy-; (5231-87-8), **69**, 221, 222

(S,S)-(-)-Diethyl tartrate: Tartaric acid, diethylester, (-)- or D-; (13811-71-7), **68**, 49

N,N-Diethyl-1,1,1-trimethylsilylamine: Silylamine, N,N-diethyl-1,1,1-trimethyl-; Silanamine, N,N-diethyl-1,1,1-trimethyl-; (996-50-9), **68**, 83

3,4-DIHYDRO-1(2H)-AZULENONE: 1(2H)-AZULENONE, 3,4-DIHYDRO-; (52487-41-9), **69**, 180

Dihydrocoumarin: 2H-1-Benzopyran-2-one, 3,4-dihydro-; (119-84-6), **69**, 73

9,10-Dihydrofulvalene: Bi-2,4-cyclopentadien-1-yl; (21423-86-9), **68**, 198

DIHYDROJASMONE, **65**, 26

3,4-DIHYDROMETHYLENE-2H-1-BENZOPYRAN: 2H-1-BENZOPYRAN, 3,4-DIHYDRO-2-METHYLENE-; (74104-13-5), **69**, 72

1,2-Dihydroxybenzene; (120-80-9), **66**, 180, 184

Dihydroxytartaric acid disodium salt hydrate; (866-17-1), **66**, 144, 146, 149

Diiodomethane; (75-11-6), **67**, 176

Diisobutylaluminum hydride; (1191-15-7), **66**, 60, 62, 66, 186, 188, 193; **69**, 15

Diisopropylamine; 2-Propanamine, N-(1-methylethyl)-; (108-18-9), **65**, 98;
66, 37, 39, 88, 194; **67**, 125; **68**, 210; **69**, 44, 56, 175, 188

DIISOPROPYL (2S,3S)-2,3-O-ISOPROPYLIDENETARTRATE: 1,3-DIOXOLANE-4,5-DICARBOXYLIC ACID, 2,2-DIMETHYL-, BIS(1-METHYLETHYL) ESTER, (4R-TRANS)-; (81327-47-1), **65**, 230

2,3-Di-O-isopropylidene-L-threitol: 1,3-Dioxolane-4,5-dimethanol, 2,2-dimethyl-, (4S-trans)-; (50622-09-8), **68**, 92

Diketene: 2-Oxetanone, 4-methylene-; (674-82-8), **66**, 109, 111, 114; **68**, 210

Dimenthyl (1S,2S)-cyclopropane-1,2-dicarboxylate, (-)-: 1,2-Cyclopropane dicarboxylic acid, bis[5-methyl-2-(1-methylethyl)cyclohexyl] ester, [1S-[1S*,2S*,5R*]], 2β,5α]-; (96149-01-8), **67**, 76

DIMENTHYL SUCCINATE, (-)-: BUTANEDIOIC ACID, BIS[5-METHYL-2-(1-METHYLETHYL)-CYCLOHEXYL]ESTER, [1R-[1α(1R*,2S*,5R*), 2β, 5α]-; (34212-59-4), **67**, 76

1,1-Dimethoxyethylene: Ethene, 1,1-dimethoxy-; (922-69-0), **65**, 98

2,2-Dimethoxypropane: Propane, 2,2-dimethoxy-; (77-76-9), **68**, 92

6,7-Dimethoxy-1,2,3,4-tetrahydro-2-[(1-tert-butoxy-3-methyl)-2-butyylimino-methyl]isoquinoline: Isoquinoline 2-[[[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]imino]methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, (S)-; (90482-03-4), **67**, 60

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride: Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-, hydrochloride; (2328-12-3), **67**, 60

N,N-Dimethylacetamide: Acetamide, N,N-dimethyl-; (127-19-5), **67**, 98; **69**, 199

Dimethyl acetylenedicarboxylate: Acetylenedicarboxylic acid, dimethyl ester;
(762-42-5), **68**, 198

3,3-Dimethylallyl bromide; (870-63-3), **66**, 76, 78, 85

Dimethylamine; (124-40-3), **68**, 162

4-(N,N-Dimethylamino)pyridine: Pyridine, 4-(dimethylamino)-;
4-Pyridinamine, N,N-dimethyl-; (1122-58-3), **65**, 12; **68**, 83, 210; **69**, 2

N,N-DIMETHYL-N'-(1-tert-BUTOXY-3-METHYL-2-BUTYL)FORMAMIDINE,
(S)-: METHANIMIDAMIDE, N'-[1-[(1,1-DIMETHYLETHOXY)METHYL]-2-
METHYLPROPYL]-N,N-DIMETHYL-, (S)-; (90482-06-7), **67**, 52, 60

N,N-Dimethylchloromethylenammonium chloride; (3724-43-4), **66**, 121, 122, 124, 126

2,2-Dimethylcyclohexane-1,3-dione: 1,3-Cyclohexanedione, 2,2-dimethyl-;
(562-13-0), **68**, 56

4,4-DIMETHYL-2-CYCLOPENTEN-1-ONE: 2-CYCLOPENTEN-1-ONE,
4,4-DIMETHYL-; (22748-16-9), **67**, 121, 205

Dimethyl diazomethylphosphonate: Phosphonic acid, (diazomethyl)-, dimethyl ester;
(27491-70-9), **65**, 119

2,2-Dimethyl-1,3-dioxane-4,6-dione, **67**, 170; **69**, 32

3,3-DIMETHYL-1,5-DIPHENYLPENTANE-1,5-DIONE: 1,5-PENTANEDIONE,
3,3-DIMETHYL-1,5-DIPHENYL-; (42052-44-8), **65**, 12

(E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL: 6,10-DODECADIEN-2-YN-
1-OL, 7,11-DIMETHYL-, (E)-; (16933-56-5), **69**, 120

1,2-DIMETHYLENECYCLOHEXANE: CYCLOHEXANE, 1,2-DIMETHYLENE;
CYCLOHEXANE, 1,2-BIS(METHYLENE)-; (2819-48-9), **65**, 90

N,N-Dimethylethanolamine: Ethanol, 2-(dimethylamino)-; (108-01-0), **68**, 162

N,N-Dimethylformamide; (68-12-2), **66**, 121, 123, 195, 197; **68**, 109

N,N-Dimethylformamide dimethyl acetal: Trimethylamine, 1,1-dimethoxy-;
Methanamine, 1,1-dimethoxy-N,N-dimethyl-; (4637-24-5), **67**, 52

Dimethyl 3,3a,3b,4,6a,7a-hexahydro-3,4,7-metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylate: 3,4,7-Metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro-, dimethyl ester; (53282-9/-6), **68**, 198

Dimethyl (E)-2-hexenedioate; (70353-99-0), **66**, 52, 53, 59

N,O-Dimethylhydroxylamine hydrochloride: Methylamine, N-methoxy-, hydrochloride; Methanamine, N-methoxy-, hydrochloride; (6638-/9-5), **67**, 69

N,N-Dimethylisobutyramide, **66**, 117, 118

Dimethyl (2S,3S)-2,3-O-isopropylidenetartrate: 1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester, (4R-trans)- or (4S-trans)-; (37031-29-1) or (37031-30-4), **65**, 230; **68**, 92

Dimethyl malonate; (108-59-8), **66**, 76, 78, 85

Dimethyl methoxymethylenemalonate: Malonic acid, (methoxymethylene)-, dimethyl ester: Propanedioic acid, (methoxymethylene)-, dimethyl ester; (22398-14-7), **65**, 98

1,3-DIMETHYL-3-METHOXY-4-PHENYLAZETIDINONE: 2-AZETIDINONE, 3-METHOXY-1,3-DIMETHYL-4-PHENYL-; (82918-98-7), **65**, 140

1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid, **66**, 38

2,2-Dimethyl-4-oxopentanal: Pentanal, 2,2-dimethyl-4-oxo-; (61031-76-3), **67**, 121

Dimethylphenylsilane: Silane, dimethylphenyl-; (766-77-8), **69**, 46, 48

N,N'-Dimethylpropyleneurea (DMPU); (7226-23-5), **66**, 45, 91, 94; **69**, 49

Dimethyl sulfate; (77-78-1), **67**, 13

Dimethyl sulfide, **66**, 211

Dimethyl sulfoxide, **66**, 15, 17

1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone; (7226-23-5), **69**, 49

(1R)-9,9-DIMETHYLTRICYCLO[6.1.1.0^{2,6}]DECA-2,5-DIENE, **68**, 220

1,9-DIMETHYL-8-(TRIMETHYLSILYL)BICYCLO[4.3.0]NON-8-EN-2-ONE, **66**, 8

(E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE: 5,9-UNDECADIEN-1-YNE,
6,10-DIMETHYL-, (E)-; (22850-55-1), **69**, 120

DINAPHTHO[2,1-D:1'2'-f][1,3,2]DIOXAPHOSPHEPIN, 4-HYDROXY-4-OXIDE,
R(-)-, **67**, 1

DINAPHTHO[2,1-d:1'2'-f][1,3,2]DIOXAPHOSPHEPIN, 4-HYDROXY-4-OXIDE,
S(+)-, **67**, 1

Dinaphtho[2,1-d:1'2'-f]dioxaphosphopin, 4-methoxy 4-oxide, **67**, 13

1,3-Dioxane, 2-(bromomethyl)-2-(chloromethyl)-, **65**, 32

1,4-Dioxane, 2,3-dichloro-, trans-, **65**, 68

1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, trans-, **65**, 68

1,4-Dioxane, 2,3-bis(1,1-dimethylethoxy)-, cis-, , **65**, 68

1,3-Dioxane-4,6-dione, 2,2-dimethyl-, **67**, 170

1,3-Dioxane-4,6-dione, 5-(hexahydro-2H-azepin-2-ylidene)-2,2-dimethyl-
67, 170

6,10-Dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile, 2-phenyl-, **65**, 32

4,8-DIOXASPIRO[2.5]OCT-1-ENE, **65**, 32

p-Dioxino[2,3-b]-p-dioxin, hexahydro, **65**, 68

[1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro, **65**, 68

1,3-Dioxolane-4,5-dicarboxylic acid, 2,2-dimethyl-, dimethyl ester,
(4R-trans)- or (4S-trans)-, **65**, 230

1,3-DIOXOLANE-4,5-DICARBOXYLIC ACID, 2,2-DIMETHYL-, BIS(1-METHYLETHYL)
ESTER, (4R-TRANS)-, **65**, 230

2,6-DIOXO-1-PHENYL-4-BENZYL-1,4-DIAZABICYCLO[3.3.0]OCTANE:
PYRROLO[3,4-c]PYRROLE-1,3(2H,3aH)-DIONE, TETRAHYDRO-
2-PHENYL-5-(PHENYLMETHYL)-, cis-; (87813-00-1), **67**, 133

Diphenylmethylchlorosilane: Silane, chloromethyldiphenyl-; (144-79-6),
67, 125

α -DIPHENYLMETHYLSILYLATION OF ESTER ENOLATES, **67**, 125

Diphenylphosphinyl chloride: Phosphinic chloride, diphenyl-; (1499-21-4),
67, 20.

Diphenyl phosphorazidate: Phosphorazidic acid, diphenyl ester; (26386-88-9), **68**, 1
2,7-DISILAOCTA-3,5-DIYNE, 2,2,7,7-TETRAMETHYL-, **65**, 52

Dsodium dihydrogen pyrophosphate; (7758-16-9), **66**, 214, 219

1,3-Dithiane; (505-23-7), **67**, 205

3,7-Dithianonane-1,9-diol: Ethanol, 2,2'-(trimethylenedithiol)di-;

Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis-;

(16260-48-3), **65**, 150

3,7-Dithianonane-1,9-dithiol: Ethanethiol, 2,2'-(trimethylenedithio)di-;

Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis-; (25676-62-4), **65**, 150

1-(1,3-Dithian-2-yl)-2-cyclohexen-1-ol: 2-Cyclohexen-1-ol, 1-(1,3-dithian-2-yl)-;

(53178-46-4), **67**, 205

DMAP, **65**, 12; **68**, 83, 210; **69**, 2

6,10-Dodecadien-2-yl-1-ol, 7,11-dimethyl-, (E), **69**, 120

5-DODECEN-2-ONE, (E)-; (81953-05-1), **68**, 210

Dowex AG 50W-XB cation exchange resin, **66**, 212, 214, 215

Enamines, α -chloro, **66**, 119

Enamines, as Diels-Alder dienophiles, **66**, 147

β -Enamino esters, **67**, 170

Enolate chlorination, **66**, 194

Enol borinate, chiral, **68**, 83

Epoxide formation, from chlorohydrin, **66**, 160

Esterase, pig liver, **69**, 20

Ester enolate alkylation, **66**, 87

Ester hydrolysis, **66**, 38, 87, 89

Estrone 3-methyl ether: 3-Methoxyestra-1,3,5(10)-trien-17-one; **69**, 131

1,2-Ethanediamine, compound with lithium acetylide, **67**, 86

1,2-Ethanediamine, N,N,N',N'-tetramethyl- (110-18-9), **68**, 32

Ethane, hexachloro- (67-72-1), **66**, 202

Ethane, 1, 1',1''-[methylidynetris(oxy)]tris-, **66**, 146

Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1), **65**, 17

Ethanedioic acid, diethyl ester, **65**, 146

Ethanethiol, 2,2'-[1,3-propanediylbis(thio)]bis-, **65**, 150

Ethanethiol, 2,2'-(trimethylenedithio)di-, **65**, 150

Ethanol, **66**, 175

Ethanol, 2-chloro-, **65**, 150

Ethanol, 2,2'-[1,3-propanediylbis(thio)]bis-, **65**, 150

Ethanol, 2,2'-(trimethylenedithio)di-, **65**, 150

Ethanone, 1-phenyl-, **65**, 6, 119

Ethene, 1,1-dimethoxy-, **65**, 98

Ethene, methoxy-, (107-25-5), **68**, 25

Ether, methyl vinyl; (107-25-5), **68**, 25

Ether, phenyl 1-phenylvinyl; (19928-57-5), **69**, 72

1-(1-Ethoxyethoxy)-1,2-propadiene, metallation, **66**, 18

1-Ethoxy-1-trimethylsiloxypropylcyclopropane: Silane, [(1-ethoxycyclopropyl)oxy]-,
trimethyl-, **67**, 210

4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE, (R), **69**, 55

Ethyl 4-bromobutyrate: Butanoic acid, 4-bromo-, ethyl ester; (2969-81-5),
67, 86

Ethyl α -(bromomethyl)acrylate; (17435-72-2), **66**, 222, 224

Ethyl chloroformate; (541-41-3), **66**, 133, 135, 141; **67**, 86

Ethyl cinnamate: 2-Propenoic acid, 3-phenyl-, ethyl ester; (103-36-6), **69**, 90
 Ethyl cyanoformate; (623-49-4), **66**, 143, 149
 ETHYL 4-CYCLOHEXYL-4-OXOBUTANOATE: CYCLOHEXANEBUTANOIC ACID, γ -OXO-, ETHYL ESTER; (54966-52-8), **65**, 17
 ETHYL CYCLOPROPYLPROPIOLATE, **66**, 173, 174
 ETHYL (E,Z)-2,4-DECADIENOATE; (3025-30-7), **66**, 22, 23, 25, 28
 Ethyl 3,4-decadienoate; (36186-28-4), **66**, 22, 28
 Ethyl decanoate: Decanoic acid, ethyl ester; (110-38-3), **67**, 125
 ETHYL DIETHOXYPROPANOATE: PROPANOIC ACID, 3,3-DIETHOXY-, ETHYL ESTER; (10601-80-6), **69**, 238
 Ethyldiisopropylamine: Triethylamine, 1,1'-dimethyl-; (7087-68-5), **68**, 162
 Ethyl 2-(diphenylmethylsilyl)decanoate: Decanoic acid, 2-(methyldiphenylsilyl)-, ethyl ester; (89638-16-4), **67**, 125
 Ethylene, **69**, 144
 Ethylenediamine, **69**, 33
 Ethylenediamine, N,N,N',N'-tetramethyl-; (110-18-9), **68**, 32
 Ethylenediaminetetraacetic acid, tetrasodium salt: Glycine, N,N'-1,2-ethanediyldis[N-(carboxymethyl)]-, tetrasodium salt, trihydrate; (67401-50-7), **65**, 166
 Ethylenediammonium diacetate; (38734-69-9), **69**, 32
 Ethyl ether, compd. with boron fluoride (BF₃) (1:1), **65**, 17
 Ethyl formate: Formic acid, ethyl ester; (109-94-4), **67**, 52
 (1-Ethyl)heptanyl 3-ketobutanoate, **68**, 210
 ETHYL α -(HEXAHYDROAZEPINYLIDENE-2)ACETATE: ACETIC ACID, (HEXAHYDRO-2H-AZEPIN-2-YLIDENE)-, ETHYL ESTER, (Z)-; (70912-51-5), **67**, 170
 ETHYL α -(HYDROXYMETHYL)ACRYLATE; (10029-04-6), **66**, 220, 222, 224

Ethyl iodide; (75-03-6), **69**, 56

ETHYL 4-IODOBUTYRATE: BUTANOIC ACID, 4-iodo-, ethyl ester;
(7425-53-8), **67**, 98

Ethylmagnesium bromide; (925-90-6), **68**, 182

Ethyl N-(2-methyl-3-nitrophenyl)formimidate, **65**, 146

ETHYL (E)-4-(4-NITROPHENYL)-4-OXO-2-BUTENOATE: 2-BUTENOIC ACID,
4-(4-NITROPHENYL)-4-OXO-, ethyl ester, **67**, 86

Ethyl oxalamidrazonate; (53085-26-0), **66**, 143, 146, 149

ETHYL 5-OXO-6-METHYL-6-HEPTENOATE, **67**, 98

Ethyl propiolate; (623-47-2), **66**, 29, 31, 36

Ethyl thioamidooxalate; (16982-21-1), **66**, 143, 145, 149

Ethyl vinyl ether: Ethene, ethoxy-, (109-92-2), **69**, 238

Ethyl vinyl ketone: 1-Penten-3-one; (1629-58-9), **69**, 189

Ethyne, **65**, 61

ETHYNYL p-TOLYL SULFONE: BENZENE, 1-(ETHYNYLSULFONYL)-4-
METHYL-, (13894-21-8), **67**, 149

-(-)-Fenchone: 2-Norbornanone, 1,3,3-trimethyl-, Bicyclo[2.2.1]heptan-2-one, 1,3,3-
trimethyl-, (1195-79-5), **68**, 14

Ferric chloride, anhydrous, **69**, 175, 177

Ferric chloride, ethanolic, **69**, 221

Finkelstein reaction, **66**, 87

Flash chromatography, **66**, 135, 196

Florisil, **66**, 197

Fluorine; (7782-41-4), **69**, 130

16 α -Fluoroestrone 3-methyl ether, **69**, 131

2-FLUOROHEXANOATE, ETHYL (R): HEXANOIC ACID, 2-FLUORO-,
ETHYL ESTER, (R)-; (124439-29-8), **69**, 10

2-FLUOROHEXANOATE, ETHYL (S): HEXANOIC ACID, 2-FLUORO-,
ETHYL ESTER, (S) ; (124439-31-2), **69**, 10

2-Fluorohexanoate, ethyl: Hexanoic acid, 2-fluoro-, ethyl ester;
(17841-31-5), **69**, 10

2-Fluorohexanoic acid, (S); (113776-26-4), **69**, 12

16 α -Fluoro-3-methoxy-1,3,5(10)-estratrien-17-one, **69**, 131

N-FLUOROPYRIDINIUM TRIFLATE; (107263-95-6), **69**, 129

Formaldehyde, **66**, 220; **68**, 206, 234, 238

Formamide, N-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-, (S)-, **67**, 52

Formamidines, N,N-dimethyl-N'-alkyl-, **67**, 52

Formic acid; (64-18-6), **68**, 109, 162

Formic acid, chloro-, ethyl ester; (541-41-3), **66**, 141; **67**, 86

Formic acid, chloro-, methyl ester, **65**, 47

Formic acid, cyano-, ethyl ester; (623-49-4), **66**, 149

Formic acid, ethyl ester, **67**, 52

Formylation, of p-tert-butylphenol, **68**, 234, 238, 243

N-Formyl-O-tert-butylvalinol, (S)-: Formamide, N-[1-[(1,1-dimethylethoxy)-
methyl]-2-methylpropyl]-, (S)-; (90482-04-5), **67**, 52

Furan; (110-60-9), **69**, 220

2-Furancarboxaldehyde; (98-01-1), **68**, 162

2-(5H)-Furanone; (497-23-4), **68**, 162

2-(5H)-Furanone, 3-methyl-; (2122-36-7), **68**, 162

Furfural: 2-Furaldehyde; (98-01-1), **68**, 162

Furyl phosphorodichloridate: Phosphorodichloridic acid, 2-furanyl ester;
(105262-70-2), **68**, 162

Furyl N,N,N',N'-tetramethyldiamidophosphate: Phosphorodiamidic acid, tetramethyl-, 2-furanyl ester; (105262-58-6), **68**, 162

Geraniol; (106-24-1), **66**, 211, 214, 219; **69**, 123

Geranyl chloride: 2,6-Octadiene, 1-chloro-3,7-dimethyl-, (E)-; (5389-87-7), **66**, 211, 212, 214, 219; **69**, 121

GERANYL DIPHOSPHATE, TRISAMMONIUM SALT, **66**, 211-213

Glucopyranoside, methyl, α -D-, **65**, 243

Glucopyranoside, methyl 4,6-O-benzylidene-, α -D-, **65**, 243

GLUCOPYRANOSIDE, METHYL 6-BROMO-6-DEOXY, 4-BENZOATE, α -D-, **65**, 243

Glucopyranoside, methyl 4,6-O-(phenylmethylene)-, α -D-, **65**, 243

Glucopyranosyl bromide, 2,3,4,6-tetraacetate, α -D-, **65**, 236

Glucopyranosyl bromide tetraacetate, α -D-, **65**, 236

Glutaric dialdehyde: Pentanedial; (111-30-8), **69**, 19

GLYCERO-D-IDO-NONONONITRILE, 4,8-ANHYDRO-2,3-DIDEOXY-, 5,6,7,9-TETRAACETATE, α -D-, **65**, 236

Glycidol: Oxiranemethanol; (556-52-5), **69**, 82

Glycine, N,N'-l,2-ethanediybis[N-(carboxymethyl)]-, tetrasodium salt, trihydrate, **65**, 166

Glycols, polyethylene, mono[p-(1,1,3,3,-tetramethylbutyl)phenyl]ether; (9002-93-1), **68**, 56

Grignard reaction, of allyl bromide, **68**, 104

Grignard reagents, reaction with acyl chlorides, **66**, 116

Grob Fragmentation, **66**, 173

Halide exchange reaction. **66**, 87

2,5-Heptadien-4-ol, 3,4,5-trimethyl-, **65**, 42

Heptanal; (111-71-7), **65**, 26

3-HEPTANONE, 4-METHYL-, (S)-, **65**, 183

5-Heptynoic acid, 7-hydroxy-, methyl ester, **67**, 193

Hexacarbonyl(1-methyl-2-propynyl)dicobalt tetrafluoroborate: Cobalt(1+),
hexacarbonyl[μ -[(2,3- η :2,3- η)-1-methyl-2-propynyl]]di-, (Co-Co),
tetrafluoroborate(1-); (62866-98-2), **67**, 141

HEXACARBONYL(PROPARGYLIUM)DICOBALT SALTS, **67**, 141

Hexachloroethane; (67-72-1), **66**, 195, 197, 202

(5Z,7E)-5,7-HEXADECADIENE, **66**, 60, 61, 63

Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine, **69**, 56

Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine: 5H-Oxazolo[3,2-a]pyridin-5-one, hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-, [2S-(2 α ,3 β ,8a β)]; (116950-01-7), **69**, 55

3,3A,3B,4,6A,7A-HEXAHYDRO-3,4,7-METHENO-7H-CYCLOPENTA[A]PENTALENE-DICARBOXYLIC ACID: 3,4,7-Metheno-7H-cyclopenta[a]pentalene-7,8-dicarboxylic acid, 3,3a,3b,4,6a,7a-hexahydro-, (61206-25-5), **68**, 198

HEXAHYDRO-4,4,7-TRIMETHYL-4H-1,3-BENZOXATHIIN: 4H-1,3-BENZOXATHIIN, HEXAHYDRO-4,4,7-TRIMETHYL-, (59324-06-0), **65**, 215

Hexamethylphosphoric triamide (HMPA); (680-31-9), **66**, 44, 45, 51, 88, 94; **69**, 48, 49

Hexanal; (66-25-1), **69**, 107

Hexanedioic acid, monomethyl ester; (627-91-8), **66**, 120

2,4-Hexenedioic acid, monomethyl ester (Z,Z)-; (61186-96-7), **66**, 184

1-Hexene, 1-iodo-, (E); (16644-98-7), **66**, 66

1-Hexene, 1-iodo-, (Z); (16538-47-9), **66**, 66

(E)-1-Hexenyl-1,3,2-benzodioxaborole: 1,3,2-Benzodioxaborole, 2-(1-hexenyl)-, (E)-; 37490-22-5), **68**, 130

(E)-1-Hexenyldiisobutylalane; (20259-40-9), **66**, 66

(E)-1-Hexenyl iodide; (16644-98-7), **66**, 63, 66

(Z)-1-Hexenyl iodide; (16538-47-9), **66**, 61, 62, 66

3-Hexylcyclobutanone, **69**, 199

1-Hexyne; (693-02-7), **66**, 66; **68**, 32, 130
 reaction with diisobutylaluminum hydride, **66**, 63

Higher order cuprates, **66**, 57

HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS, **66**, 132

Homoenolate, copper, **66**, 47

Homoenolate, titanium, **66**, 47

HOMOENOLATE, ZINC, **66**, 43

Horner-Wadsworth-Emmons reaction, **66**, 220

Hydrazine, **66**, 143; **67**, 60, 187

Hydrazine, tert-butyl, monohydrochloride, **65**, 166

Hydrazine, (1,1-dimethylethyl)-, monohydrochloride, **65**, 166

Hydroalumination of alkynes, **66**, 64

Hydroboration of alkynes, **66**, 64
 of 1-alkyne with catecholborane, **68**, 130

Hydrocinnamoyl chloride: Benzenepropanoyl chloride; (645-45-4), **69**, 180

Hydrogen; (1333-74-0), **68**, 64, 182, 228

Hydrogenation, homogeneous, directed, **68**, 64

Hydrogen chloride, **66**, 144, 146

Hydrogenolysis, **68**, 227

Hydrogen peroxide; (7722-84-1), **65**, 166; **68**, 83, 130, 162; **69**, 97

Hydrogen sulfide, **66**, 143, 145

Hydroperoxide, 1-methyl-1-phenylethyl; (80-15-9), **68**, 49

Hydroquinone: 1,4-Benzenediol; (123-31-9), **67**, 98

as diene stabilizer, **66**, 63

3-HYDROXY-1-CYCLOHEXENE-1-CARBOXALDEHYDE: 1-CYCLOHEXENE-1-CARBOXALDEHYDE, 3-HYDROXY-; (67252-14-6), **67**, 205

(S)-(+)-3-HYDROXY-2,2-DIMETHYLCYCLOHEXANONE: Cyclohexanone, 3-hydroxy-2,2-dimethyl-, (S)-; (87655-21-8), **68**, 56

Hydroxylamine, N-phenyl-, **67**, 187

α -Hydroxylation of ketones, **66**, 138

1-(HYDROXYMETHYL)CYCLOHEXANOL: CYCLOHEXANEMETHANOL, 1-HYDROXY-; (15753-47-6), **69**, 96

1-HYDROXYMETHYL-4-(1-METHYLCYCLOPROPYL)-1-CYCLOHEXENE: 1-CYCLOHEXENE-1-METHANOL, 4-(1-METHYLCYCLOPROPYL)-; (536-59-4), **67**, 176

3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE: 1-BUTANONE, 3-HYDROXY-3-METHYL-1-PHENYL-; (43108-74-3), **65**, 6, 12

1-(3-HYDROXY-2-METHYL-3-PHENYLPROPANOYL)PIPERIDINE, ERYTHRO: PIPERIDINE, 1-(3-HYDROXY-2-METHYL-1-OXO-3-PHENYLPROPYL)-, R*,R*-(±)-; (99114-36-0), **69**, 44

N-Hydroxymethylphthalimide: Phthalimide, N-(hydroxymethyl)-; 1H-Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)-; (118-29-6), **65**, 119

3-HYDROXY-2-NITROCYCLOHEXYL ACETATE, (1S,2S,3R): 1,3-CYCLOHEXANEDIOL, 2-NITRO-, 1-ACETATE, [1S-(1 α ,2 β ,3 α)]-; (108186-61-4), **69**, 19

3-Hydroxy-1-nonene: 1-Nonen-3-ol; (21964-44-3), **68**, 210

(2S*,3S*)-3-HYDROXY-3-PHENYL-2-METHYLPROPANOIC ACID, **68**, 83

(1-Hydroxy-2-propenyl)trimethylsilane, **66**, 14, 15

3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE: 4-OCTANONE, 3-HYDROXY-2,2,3-TRIMETHYL-; (85083-71-2), 69, 114

Hydrozirconation of alkynes, **66, 64**

Hypervalent iodine compounds, **66, 138**

Imines, reduction by diisobutylaluminum hydride, **66, 189**

5H-Inden-5-one, 1,2,3,3a,4,6-hexahydro-, **67, 163**

INDOLE, 4-NITRO-, **65, 146**

INTRAMOLECULAR ACYLATION OF ALKYSILANES, **66, 87**

INVERSE ELECTRON DEMAND DIELS-ALDER, **65, 98**

Iodine; (7553-50-2), **68, 198**

Iodine, hypervalent, **68, 175**

Iodine, phenylbis(trifluoroacetato-O); (2712-78-9), **66, 141**

Iodobenzene diacetate, **66, 136**

Iodobenzene dichloride, **66, 137**

6-Iodo-3,4-dimethoxybenzaldehyde cyclohexylimine: Cyclohexanamine, N-[(2-iodo-4,5-dimethoxyphenyl)methylene]-; (61599-78-8), **65, 108**

Iodomethane; (74-88-4), **68, 56, 116, 162**

Iodosobenzene diacetate: Benzene, (diacetoxyiodo)-; (3240-94-4), **68, 175**

o-Iodotoluene; (615-37-2), **66, 67, 68, 74**

1-Iodo-3-trimethylsilylpropane; (18135-48-3), **66, 87, 88, 91, 94**

Ion exchange chromatography, **66, 212, 214, 215**

Iron pentacarbonyl, **66, 99**

Isobutene; (115-11-7), **67, 52**

Isobutyl chloride, **69, 107**

Isobutyl chloroformate, **66, 135**

Isobutylmagnesium chloride, **69, 106**

(R)-Isobutyloxirane, **66**, 165

Isoindole-1,3-(2H)-dione, 2-(bromomethyl)-, 1H-, **65**, 119

Isoindole-1,3-(2H)-dione, 2-(hydroxymethyl)-, 1H-, **65**, 119

(S)-Isoleucine, **66**, 153

Isomenthol, (+)-: Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1S-(1 α ,2 β ,5 β)];

(23263-97-8), **65**, 81

Isomenthone, (+)-: Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R-cis)-;

(1196-31-2), **65**, 81

ISOPRENE; (78-79-5), **67**, 48

(Isopropoxydimethylsilyl)methyl chloride: Silane, (chloromethyl)isopropoxydimethyl-;

(18171-11-4), **69**, 96

1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol, **69**, 96

Isopropyl alcohol, titanium (4+) salts; (546-68-9), **65**, 230; **67**, 180; **68**, 49

Isopropylideneacetophenone: 2-Buten-1-one, 3-methyl-1-phenyl-;

(5650-07-7), **65**, 12

Isopropylidene α -(hexahydroazepinylidene-2)malonate: 1,3-Dioxane-4,6-

dione, 5-(hexahydro-2H-azepin-2-ylidene)-2,2-dimethyl-; (70192-54-8),

67, 170

(R)-Isopropyloxirane, **66**, 165

Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy, hydrochloride, **67**, 60

Isoquinoline, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-, (S)-, **67**, 60

Jones' reagent, **68**, 175

Ketones, preparation from carboxylic acid, **66**, 119

β -Lactams, **65**, 140

Lactic acid, 2-methyl-, methyl ester; (2110-78-3), **66**, 114

Lead dioxide: Lead oxide; (1300-60-0), **65**, 166

Lead oxide, **65**, 166

Lead tetraacetate; (546-67-8), **69**, 190

(S)-Leucine, **66**, 153

Leucine, N-carboxy-, N-tert-butyl ester, L-, **67**, 69

L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-, **67**, 69

Lindlar catalyst (modified), **60**, 102

Lipase (P-30), **69**, 12

Lipase (*P. fluorescens*); (9001-62-1), **69**, 3

Lipshutz reagents, **66**, 57

Lithiobutadiyne, **65**, 52

2-Lithiofuran, **69**, 221

2-Lithiothiophene, **69**, 80

Lithium, **66**, 127, 128; **67**, 193

Lithium acetate dihydrate: Acetic acid, lithium salt, dihydrate; (6108-17-4),
67, 105; **69**, 38

Lithium acetylide, **68**, 14

ethylenediamine complex: 1,2-Ethanediamine, compound
with lithium acetylide ($\text{Li}(\text{C}_2\text{H})$); (6867-30-7), **67**, 86

Lithium aluminum hydride, **66**, 160; **67**, 69; **68**, 92; **69**, 15, 154

Lithium, butyl-, **65**, 98, 108, 119; **66**, 14, 16, 37, 39, 88, 194, 196; **67**, 44, 48

Lithium, tert-butyl-, **66**, 15, 16, 18, 67, 69; **67**, 60, 210

Lithium chloride; (7447-41-8), **68**, 109; **69**, 38

Lithium diisopropylamide, **65**, 98; **66**, 37, 88, 194; **67**, 125; **68**, 210

Lithium fluoride, **67**, 133

Lithium hydroxide; (1310-66-3), **68**, 83
Lithium, methyl-, **65**, 47, 140; **67**, 86, 125
Lithium tetrafluoroborate, **66**, 52, 54
Lithium 2,2,6,6-tetramethylpiperidide (LTMP), **67**, 76
Lithium tri(tert-butoxy)aluminum hydride, **66**, 122, 124
Lyophilization, **66**, 212-214

MACROCYCLIC SULFIDES, **65**, 150

Magnesium, **66**, 118, 175; **68**, 1, 104, 116; **69**, 2, 96, 107
Magnesium ethoxide, **66**, 175
Maleimide, N-phenyl-, **67**, 133
Malonic acid, cyclic isopropylidene ester, **67**, 170
Malonic acid, dimethyl ester; (108-59-8), **66**, 85
Malonic acid, (methoxymethylene)-, dimethyl ester, **65**, 98
Malonic ester alkylation, **66**, 75
Malononitrile, benzylidene-, **65**, 32
Manganese dioxide; (1313-13-9), **68**, 109; **69**, 38; **69**, 38
D-Mannitol; (69-65-8), **69**, 83
MELDRUM'S ACID: 2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE; MALONIC
ACID, CYCLIC ISOPROPYLIDENE ESTER; 1,3-DIOXANE-4,6-DIONE,
2,2-DIMETHYL-; (2033-24-1), **67**, 170; **69**, 33
p-Mentha-6,8-dien-2-one; (6485-40-1), **66**, 13
3H-3a,6-METHANO-2,1-BENZISOTHIAZOLE,4,5,6,7-TETRAHYDRO-8,8-
DIMETHYL-2,2-DIOXIDE, (3aS); (60886-80-8), **69**, 154
4H-4a,7-METHANOOXAZIRINO[3.2-I][2.1]BENZISOTHIAZOLE, TETRAHYDRO-
9,9-DIMETHYL-3,3-DIOXIDE, [4aS-(4 α ,7 α ,8aR*)]; (104322-63-6), **69**, 158
p-MENTH-4-(8)-EN-3-ONE, (R)-(+)-, **65**, 203, 215

Menthol, (-)-: Cyclohexanol, 5-methyl-2-(1-methylethyl)-. [1R-(1 α ,2 β ,5 α)]-:

(2216-51-5), **67**, 76; **68**, 155

(-)-MENTHYL CINNAMATE: 2-Propenoic acid, 3-phenyl-, 5-methylethyl)cyclohexyl ester. [1R-(1 α ,2 β ,5 α)]-: (16205-99-5). **68**, 155

(-)-MENTHYL NICOTINATE: 3-Pyridinecarboxylic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-(1 α ,2 β ,5 α)]-, **68**, 155

2-(1-Mercapto-1-methylethyl)-5-methylcyclohexanol: Cyclohexanol-2-(1-mercapto-1-methylethyl)-5-methyl-, [1R-(1 α ,2 α ,5 α)]-;
(79563-68-1); [1R-(1 α ,2 β ,5 α)] (79563-59-0); [1S-(1 α ,2 α ,5 β)]-;
(79563-67-0), **65**, 215

Mercuric chloride; (7487-94-7), **68**, 148

Mercurisulfonylation, of cyclohexa-1,3-diene, **68**, 148

Mercury, **66**, 96

Mercury(II) oxide, red; (21908-53-2), **67**, 205

METHACRYLOYL CHLORIDE: 2-PROPENOYL CHLORIDE, 2-METHYL-;
(920-46-7), **67**, 98

Methanamine, 1,1-dimethoxy-N,N-dimethyl-, **67**, 52

Methanamine, N-methoxy-, hydrochloride, **67**, 69

Methanamine, N-(phenylmethylene)-, **65**, 140

Methane, dibromo-, **65**, 81

Methane, nitro-; (75-52-5), **68**, 8

Methane, nitro-, ion(1-), sodium; (25854-38-0), **68**, 8

METHANESULFONYL BROMIDE, BROMO-, **65**, 90

Methanesulfonyl chloride; (124-63-0), **66**, 1, 3, 186, 187, 193

Methanethiol, **66**, 188

Methanimidamide, N'-[1-[(1,1-dimethylethoxy)methyl]-2-methylpropyl]-N,N-dimethyl-, (S)-, **67**, 52, 60

Methanol; (67-56-1), **66**, 85, 182, 184

4-Methoxyaniline: p-Anisidine; (104-94-9), **68**, 188

4 METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a OCTAHYDRO 2,3
BENZOPYRONE, (4RS,4aRS,6RS,8aRS), **69**, 31

4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a-OCTAHYDRO-2,3-
BENZOPYRONE, (4S,4aS,6S,8aS), **69**, 31

4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a-OCTAHYDRO-2,3-
BENZOPYRONE, (4R,4aR,6R,8aR), **69**, 31

6-Methoxy-7-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene: 2-Naphthalene-
carboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester;
(78112-34-2), **65**, 98

4-METHOXY-3-PENTEN-2-ONE: 3-PENTEN-2-ONE 4-METHOXY-;
(2845-83-2), **67**, 202

1-(4-METHOXYPHENYL)-1,2,5,6-TETRAHYDROPYRIDINE, **68**, 188

N-(4-Methoxyphenyl)-Z-4-(trimethylsilyl)-3-butenamine, **68**, 188

α -Methoxy- α -trifluoromethylphenylacetyl chloride, (S)-(+)-, **69**, 15

1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene: Silane, [(3-methoxy-1-methylene-
2-propenyl)oxy]trimethyl-, (59414-23-2), **67**, 163

3-Methoxy-17-trimethylsiloxy-1,3,5(10),16-estratetraene, **69**, 131

1-Methoxyvinyl lithium, **68**, 25

1-(Methoxyvinyl)trimethylsilane: Silane, (1-methoxyethenyl)trimethyl-,
(79678-01-6), **68**, 25

Methyl acrylate; (96-33-3), **66**, 54, 59
dimerization by Pd(II), **66**, 52

Methylamine, N-benzylidene-, **65**, 140

Methylamine, N-methoxy-, hydrochloride, **67**, 69

Methyl (E)-3-(benzenesulfonyl)prop-2-enoate, **69**, 169

METHYL (Z)-3-(BENZENESULFONYL)PROP-2-ENOATE: 2-PROPENOIC ACID.

3-(PHENYLSULFONYL)-, METHYL ESTER, (Z)-; (91077-67-7), 69, 169

METHYL 4-O-BENZOYL-6-BROMO-6-DEOXY- α -D-GLUCOPYRANOSIDE:

**GLUCOPYRANOSIDE, METHYL 6-BROMO-6-DEOXY, 4-BENZOATE,
 α -D-; (10368-81-7), 65, 243**

Methyl 4,6-O-benzylidene- α -D-glucopyranoside: Glucopyranoside, methyl

**4,6-O-benzylidene- α -D-; α -D-glucopyranoside, methyl 4,6-O-
(phenylmethylene)-; (3162-96-7), 65, 243**

N-Methylbenzylidenimine: Methylamine, N-benzylidene-; Methanamine,

N-(phenylmethylene)-; (622-29-7), 65, 140

4-Methylbicyclo[2.2.2]octane-2,6-dione; (119986-98-0), 69, 175

Methyl 4-bromo-1-butanimidate hydrochloride, 67, 193

(S)-(+)-2-METHYLBUTANAL: BUTANAL. 2-METHYL-. (S)-: (1730-97-8).

69, 212, 215

(S)-(-)-2-Methyl-1-butanol: 1-Butanol, 2-methyl-, (S)-; (1565-80-6), 69, 212, 215

2-Methyl-2-butene: 2-Butene, 2-methyl-; (513-35-9). 65, 159

(3-Methyl-2-butenyl)propanedioic acid, dimethyl ester;

(43219-18-7), 66, 78, 85

(3-Methyl-2-butenyl)(2-propynyl)propanedioic acid, dimethyl ester, 66, 76

O-METHYLCAPROLACTIM: 2H-AZEPINE, 3,4,5,6-TETRAHYDRO-7-

METHOXY-; (2525-16-8); 67, 170

Methyl carbamate: Carbamic acid, methyl ester; (598-55-0), 65, 159

METHYL 4-CHLORO-2-BUTYNOATE: 2-BUTYNOIC ACID, 4-CHLORO-, METHYL

ESTER; (41658-12-2), 65, 47

METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE: ACETIC ACID,

CHLOROCYCLOPROPYLIDENE METHYL ESTER; (82979-45-1), 69, 148, 149

Methyl chloroformate: Formic acid, chloro-, methyl ester;

Carbonochloridic acid, methyl ester; (79-22-1), **65**, 47

Methyl cinnamate: Cinnamic acid, methyl ester; (103-26-4), **68**, 155

Methyl (E)-crotonate; (623-43-8), **66**, 38, 39, 41, 42

2-Methylcyclohexane-1,3-dione: 1,3-Cyclohexanedione, 2-methyl-;

(1193-55-1), **68**, 56

3-Methylcyclohexanone-3-acetic acid: Cyclohexaneacetic acid, 1-methyl-3-oxo-, (\pm)-;

(119986-97-9), **69**, 173

1-Methylcyclohexene: Cyclohexene, 1-methyl-, (591-49-1), **65**, 90

3-Methyl-2-cyclohexen-1-one; (1193-18-6), **66**, 37, 39, 42; **69**, 174

cis-1-METHYLCYCLOPENTANE-1,2-DICARBOXYLIC ACID:

1,2-Cyclopentanedicarboxylic acid, 1-methyl-, cis-(\pm)-; (70433-31-7), **68**, 41

1-Methyl-1-cyclopentene: Cyclopentene, 1-methyl-, (693-89-0), **68**, 41

Methyl N,N-dichlorocarbamate: Carbamic acid, dichloro-, methyl ester;

(16487-46-0), **65**, 159

Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate, **66**, 37

Methyl 1,1'-dinaphthyl-2,2'-diyl phosphate, (R)-(-)-: Dinaphtho[2,1-d:1'2'-f]di-

oxaphosphopin, 4-methoxy-, 4-oxide, (R)-; (86334-02-3), **67**, 13

METHYLENATION OF CARBONYL COMPOUNDS, **65**, 81

3-Methylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid,

dimethyl ester, **66**, 78

3-METHYLENE-CIS-p-MENTHANE, (+)-: (CYCLOHEXANE,

5-METHYL-1-METHYLENE-2-(1'-METHYLETHYL)-, R,R-), **65**, 81

1-METHYL-2-ETHYNYL-endo-3,3-DIMETHYL-2-NORBORNANOL;

(1195-79-5), **68**, 14

3-METHYL-2(5H)-FURANONE: 2(5H)-Furanone, 3-methyl-, **68**, 162

2-(3-Methylfuryl) tetramethylaminophosphate: Phosphorodiamidic acid, tetramethyl-, 3-methyl-2-furanyl ester; (105262-59-7), **68**, 162

Methyl α -D-glucopyranoside: Glucopyranoside, methyl, α -D-; α -D-glucopyranoside, methyl; (97-30-3), **65**, 243

4-METHYL-3-HEPTANONE, (S)-(+)-: 3-HEPTANONE, 4-METHYL-, (S)-; (51532-30-0), **65**, 183

4-Methyl-3-heptanone SAMP-hydrazone, (S)-(+)-: 1-Pyrrolidinamine, N-(1-ethyl-2-methylpentylidene)-2-(methoxymethyl)-, [S-[R*,R*-(Z)]-; (69943-24-4), **65**, 183

METHYL 7-HYDROXYHEPT-5-ENOATE: 5-HEPTYNOIC ACID, 7-HYDROXY-, METHYL ESTER; (50781-91-4), **67**, 193

Methyl 2-hydroxyisobutyrate; (2110-78-3), **66**, 110, 111, 114

Methyl 3-hydroxy-2-methylenepentanoate: Pentanoic acid, 3-hydroxy-2-methylene-, methyl ester; (18052-21-6), **68**, 64

METHYL anti-3-HYDROXY-2-METHYLPENTANOATE: Pentanoic acid, 3-hydroxy-2-methyl-, methyl ester, (R*,R*)-(\pm)-; (100992-75-4), **68**, 64

Methyl iodide: Iodomethane; (74-88-4), **68**, 56, 116, 162

Methyl lithium: Lithium, methyl-; (917-54-4), **65**, 47, 140; **66**, 97, 100; **67**, 86, 125; **68**, 220

Methyl lithium, low halide, **66**, 53, 55

Methylmagnesium bromide, **67**, 125

Methylmagnesium chloride, **66**, 1-3

[(Methyl)(methoxy)carbene]pentacarbonyl chromium(0): Chromium, pentacarbonyl(1-methoxyethylidene)-, (OC-6-21)-; (20540-69-6), **65**, 140

METHYL N-(2-METHYL-2-BUTENYL)CARBAMATE: CARBAMIC ACID, (2-METHYL-2-BUTENYL)-, METHYL ESTER; (86766-65-6), **65**, 159

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (2R,5R)-: Cyclohexanone,

5-methyl-2-(1-methyl-1-phenylethyl)-, (2R-trans)-; (57707-92-3), **65**, 203

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (2S,5R)-: Cyclohexanone, 5-methyl-2-(1-methyl-1-phenylethyl)-, (2S-cis)-; (65337-06-6), **65**, 203

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate, (1R,2S,5R)-: Acetic acid, chloro-, 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester, [1R-(1 α ,2 β ,5 α)]-; (71804-27-8), **65**, 20

5-Methyl-2-[1-methyl-1-(phenylmethylthio)ethyl]cyclohexanone, cis- and trans-; **65**, 215

5-Methyl-2-(1-methyl-1-thioethyl)cyclohexanol, **65**, 215

N-Methylmorpholine, **66**, 133, 135

Methyl nicotinate: Nicotinic acid, methyl ester; (93-60-7), **68**, 155

2-Methyl-3-nitroaniline: o-Toluidine, 3-nitro-; Benzeneamine, 2-methyl-3-nitro-; (603-83-8), **65**, 146

2-METHYL-4'-NITROBIPHENYL, **66**, 67, 68

(R)-METHYLOXIRANE; (15448-47-2), **66**, 160, 161, 163, 164, 172

METHYL 6-OXODECANOATE; (61820-00-6), **66**, 116, 117, 120, 123

METHYL 2-OXO-5,6,7,8-TETRAHYDRO-2H-1-BENZOPYRAN-3-CARBOXYLATE: 2H-1-BENZOPYRAN-3-CARBOXYLIC ACID, 5,6,7,8-TETRAHYDRO-2-OXO-, METHYL ESTER; (85531-80-2), **65**, 98

(E)-3-Methyl-3-penten-2-one, **66**, 11

(Z)-3-Methyl-3-penten-2-one, **66**, 11

3-METHYL-2-PENTYL-2-CYCLOPENTEN-1-ONE: 2-CYCLOPENTEN-1-ONE, 3-METHYL-2-PENTYL-; (1128-08-1), **65**, 26

3-Methyl-1-phenyl-1,3-butadiene, **69**, 91

2-METHYL-2-PHENYL-4-PENTENAL: 4-PENTENAL, 2-METHYL-2-PHENYL-; (24401-39-6), **65**, 119

N-Methylpiperidine: 1-Methylpiperidine; (626-67-5), **67**, 69

2-Methylpropane-2-thiol; (75-66-1), **66**, 108, 109, 111, 114

Methyl propiolate: 2-Propynoic acid, methyl ester; (922-67-8), **69**, 169

2-(1-METHYL-2-PROPYNYL)CYCLOHEXANONE, **67**, 141

Methyl tiglate; (6622-76-0), **66**, 88, 91, 94

Methyl p-tolyl sulfide: Sulfide, methyl p-tolyl; Benzene, 1-methyl-4-(methylthio)-; (623-13-2), **68**, 49

(S)-(-)-MFTHYL p-TOLYL SULFOXIDE: Benzene, 1-methyl-4-(methylsulfinyl)-. (S)-; (5056-07-5), **68**, 49

Methyltriisopropoxytitanium: Titanium, triisopropoxymethyl-; Titanium, methyltris(2-propanolato)-, (T-4)-; (19006-13-8), **67**, 180

4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE: TRICYCLO[3.2.1.0^{2,7}]OCTANE-6,8-DIONE, 2-METHYL-; (119986-99-1), **69**, 173, 175

1-Methyl-1-(trimethylsilyl)allene, **66**, 1, 2, 4

2-METHYL-2-UNDECENE: 2-UNDECENE, 2-METHYL-; (56888-88-1), **67**, 125

2-METHYL-2-VINYLCYCLOPENTANONE; (88729-76-4), **66**, 87, 88, 90, 91, 94

trans-3-METHYL-2-VINYLCYCLOHEXANONE, **66**, 95, 98

Methyl vinyl ether: Ether, methyl vinyl; Ethene, methoxy-; (107-25-5), **68**, 25; **69**, 240

MICHAEL ADDITION, APROTIC, **66**, 37, 41

Monolithiation, of acetylene, **68**, 14

Monolithium acetylide: Lithium acetylide; (1111-64-4), **68**, 14

Monolithium acetylide; reaction apparatus, **68**, 22

cis,cis-Monomethyl muconate; (61186-96-7), **66**, 180, 184

cis,cis-MONOMETHYL MUCONATE FROM 1,2-DIHYDROXYBENZENE, **66**, 180

Morpholine; (110-91-8), **67**, 222

Morpholine 4-chloro-, **67**, 222

Mucochloric acid; 2-Butenoic acid, 2,3-dichloro-4-oxo-, (Z)-; (87-56-9), **69**, 205

MYRCENE: 1,6-OCTADIENE, 7-METHYL-3-METHYLENE-; (123-35-3),

67, 44

2-Naphthalenecarboxylic acid, 5,6,7,8-tetrahydro-3-methoxy-, methyl ester, **65, 98**

Nickel acetylacetonate: Nickel, bis(2,4-pentanedionato-O,O'), (SP-4-1);

(3264-82-2), **67, 170**

Nickel-catalyzed aryl-aryl coupling, **66, 70**

m-Nitrobenzaldehyde: Benzaldehyde, 3-nitro-; (99-61-6), **67, 180**

p-Nitrobenzoyl chloride: Benzoyl chloride, 4-nitro-; (122-04-3), **67, 86**

2-Nitrocyclohexane-1,3-diol, (1R,2r,3S): 1,3-Cyclohexanediol, 2-nitro-,

(1 α ,2 β ,3 α)-; (38150-01-5), **69, 19**

4-NITROINDOLE: INDOLE, 4-NITRO-; (4769-97-5), **65, 146**

Nitromethane: Methane, nitro-; (75-52-5), **68, 8; 69, 19**

3'-NITRO-1-PHENYLETHANOL: BENZENEMETHANOL, α -METHYL-3-NITRO-;

(5400-78-2), **67, 180**

1-Nitroso-2-methoxymethylpyrrolidine, (S)-: Pyrrolidine, 2-(methoxymethyl)-

1-nitroso-, (S)-; (60096-50-6), **65, 183**

Nitrosonium tetrafluoroborate, **66, 54**

Nitroso-tert-octane: Pentane, 2,2,4-trimethyl-4-nitroso-; (31044-98-1), **65, 166**

(1R)-Nopadiene: 2-Norpinene, 6,6-dimethyl-2-vinyl-, (+); (30293-06-2), **68, 220**

(1R)-(-)-Nopol: Bicyclo[3.1.1]hept-2-ene-2-ethanol, 6,6-dimethyl-, (1R)-; (35836-73-8),

68, 220

2-Norbornanone, 1,3,3-trimethyl-; (1195-79-5), **68, 14**

1,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl, [R-(E)]-, **67, 33**

2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl, (E)-, **67, 33, 44**

2,6-Octadien-1-amine, N,N-diethyl-3,7-dimethyl-, (Z)-, **67, 33, 48**

1,6-Octadiene, 7-methyl-3-methylene-, **67**, 44

4-Octanone, 3-hydroxy-2,2,3-trimethyl; (85083-71-2), **69**, 114

6-Octenal, 3,7-dimethyl-, (R)-(+)-, **67**, 33

1-Octene; (111-66-0), **69**, 199

(Z)-2-Octen-1-ol, **69**, 108

tert-Octylamine: 2-Pentamine, 2,4,4-trimethyl-; (107-45-9), **65**, 166

N-tert-Octyl-O-tert-butylhydroxylamine: 2-Pentamine, N-(1,1-dimethylethoxy)-2,4,4-trimethyl-; (68295-32-9), **65**, 166

1-Octyn-3-ol; (818-72-4), **66**, 22, 23, 28

2-Octyn-1-ol; (20739-58-6), **69**, 106

Organoaluminum compounds, reaction with imino carbocations, **66**, 189

Orthoester Claisen rearrangement, **66**, 22

Orthoformic acid, triethyl ester, **65**, 146

6-Oxabicyclo[3.1.0]hex-2-ene, **67**, 114

Oxalic acid, diethyl ester, **65**, 146

Oxalyl chloride; (79-37-8), **66**, 15, 17, 21, 89, 94, 117, 121, 123

1,3-OXATHIANE, **65**, 215

Oxaziridine, 3-phenyl-2-(phenylsulfonyl)-; (63160-13-4), **66**, 203, 210

Oxazolidinone, chiral auxiliary, **68**, 83

2H-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (E)- (114633-68-0), **69**, 188

Oxidation, of diol, with Jones' reagent, **68**, 175

Oxidation, sulfide, enantioselective, **68**, 56

OXIDATIVE CLEAVAGE, OF AROMATIC RINGS; **66**, 180

with ruthenium (IV), **68**, 41

Oximes, mesylation, **66**, 185

Oxirane, methyl; (15448-47-2), **66**, 172

4-Oxo-1-(benzenesulfonyl)-cis-bicyclo[4.3.0]non-2-ene, **67**, 163

6-OXODECANAL; (63049-53-6), **66**, 121, 122, 126

6-Oxodecanoic acid; (4144-60-9), **66**, 122, 123, 126

5-Oxohexanoic acid: Hexanoic acid, 5-oxo-; (3128-06-1), **69**, 55

Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate, (37222-66-5), **69**, 160, 229

Oxonium, trimethyl-, tetrafluoroborate (1-), **65**, 140

(1-OXO-2-PROPENYL)TRIMETHYLSILANE, **66**, 14-16, 18

3-(1-Oxopropyl)-4-(S)-phenylmethyl-2-oxazolidinone: 2-Oxazolidinone, 3-(1-oxopropyl)-4-(phenylmethyl)-, (S)-; (101711-78-8), **68**, 83

Ozone (10028-15-6), **65**, 183

Palladium acetate: Acetic acid, palladium(2+) salt; (3375-31-3), **67**, 105; **68**, 109, 138; **69**, 38, 39

Palladium, benzylchlorobis(triphenylphosphine)-, trans-, **67**, 86

Palladium-catalyzed aryl-aryl coupling, **66**, 70

PALLADIUM-CATALYZED ALLYLIC AMINATION, **67**, 105

PALLADIUM-CATALYZED CHLOROACETOXYLATION, **67**, 105

PALLADIUM-CATALYZED COUPLING OF ACID CHLORIDES WITH ORGANOTIN REAGENTS, **67**, 86

PALLADIUM-CATALYZED COUPLING OF ARYL HALIDES, **66**, 67

PALLADIUM-CATALYZED syn-ADDITION OF CARBOXYLIC ACIDS, **67**, 114

Palladium(II) chloride; (7647-10-1), **67**, 121; **68**, 130

Palladium, chloro(phenylmethyl)bis(triphenylphosphine)-, **67**, 86

Palladium-on-carbon, **68**, 227

Palladium sponge, **66**, 54

Palladium, tetrakis(acetonitrile)-, tetrafluoroborate, **66**, 52

Palladium, tetrakis(triphenylphosphine)-; (14221-01-3),
66, 61, 62, 66, 68, 69, 74; **67**, 86, 98, 105, 114; **68**, 116

Paraformaldehyde: Poly(oxymethylene); (9002-81-7), **65**, 215;
66, 220, 221; **68**, 243; **69**, 122, 189

1,4-Pentalenediol, octahydro-, (1 α ,3 α ,4 α ,6 α)-; (17572-86-0), **68**, 175

1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENE: 1,3-CYCLOPENTADIENE,
1,2,3,4,5-PENTAMETHYL-; (4045-44-7), **65**, 42

Pentanal; (110-62-3), **69**, 227

Pentanal, 2,2-dimethyl-4-oxo-, **67**, 121

2-Pentanamine, N-(1,1-dimethylethoxy)-N-(1,1-dimethylethyl)-
2,4,4-trimethyl-, **65**, 166

2-Pentanamine, N-(1,1-dimethylethoxy)-2,4,4-trimethyl-, **65**, 166

2-PENTANAMINE, N-(1,1-DIMETHYLETHYL)-2,4,4-TRIMETHYL-, **65**, 166

2-Pentanamine, 2,4,4-trimethyl-, **65**, 166

1,5-PENTANEDIONE, 3,3-DIMETHYL-1,5-DIPHENYL-, **65**, 12

Pentane, 2,2,4-trimethyl-4-nitroso-, **65**, 166

3-Pentanone SAMP-hydrazone: 1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)-, (59963-36-7), **65**, 183

4-PENTENAL, 2-METHYL-2-PHENYL-, **65**, 119

4-Penten-2-ol, 1-(phenylmethoxy); (58931-16-11), **69**, 80

3-Penten-2-one, 4-methoxy-, **67**, 202

(E)-3-PENTYL-2-NONENE-1,4-DIOL, **69**, 106

Perchloric acid, silver(1+) salt, monohydrate, **67**, 33

Performic acid, oxidation of furfural, **68**, 162

PERRILLYL ALCOHOL, (S)-(-)-: 1-CYCLOHEXENE-1-METHANOL, 4-(1-METHYLETHENYL)-; (536-59-4), **67**, 176

- 1-PHENOXY-1-PHENYLETHENE: ETHER, PHENYL 1-PHENYLVINYL;
(19928-57-5), **69**, 72
- L-Phenylalanine; Phenylalanine, (S)-; (63-91-2), **69**, 77
- (S)-Phenylalanol; (3182-95-4), **68**, 77
- Phenyl benzeneselenosulfonate: Benzenesulfonoselenoic acid, Se-phenyl
ester; (60805-71-2), **67**, 157
- Phenyl benzoate: Benzoic acid, phenyl ester; (93-99-2), **69**, 73
- PHENYLCYCLOHEXANOL, (+)-(1S,2R)-trans-2: CYCLOHEXANOL, 2-PHENYL-,
(1S-trans)-; (34281-92-0), **69**, 1
- PHENYLCYCLOHEXANOL, (-)-(1R,2S)-trans-2: CYCLOHEXANOL, 2-PHENYL-,
(1R-trans)-; (98919-68-7), **69**, 1
- 2-Phenylcyclohexyl chloroacetate, trans, **69**, 3
- N-Phenylhydroxylamine: Hydroxylamine, N-phenyl-; Benzeneamine,
N-hydroxy-; (100-65-2), **67**, 187
- N-Phenylmaleimide: Maleimide, N-phenyl-; 1H-Pyrrole-2,5-dione, 1-phenyl-;
(941-69-5), **67**, 133
- 8-PHENYLMENTHOL, (-)-: CYCLOHEXANOL, 5-METHYL-2-(1-METHYL-
1-PHENYLETHYL)-, [1R-(1 α ,2 β ,5 α)]-; (65253-04-5), **65**, 203
- (S)-4-(PHENYLMETHYL)-2-OXAZOLIDINONE: 2-Oxazolidinone, 4-(phenylmethyl)-,
(S); (90719-32-7), **68**, 77, 83
- (1Z,3E)-1-PHENYL-1,3-OCTADIENE: Benzene, 1,3-octadienyl-, (Z,E)-; (39491-66-2),
68, 130
- 3-PHENYL-4-PENTENAL, **66**, 29, 31, 36
- 2-Phenyl-N-(phenylmethylene)-1-propen-1-amine: 1-Propen-1-amine,
2-Phenyl-N-(phenylmethylene)-; (64244-34-4), **65**, 119
- (E)-3-[(E)-3-Phenyl-2-propenoxy]acrylic acid; (88083-18-5), **66**, 30, 31, 36
- 3-Phenylpropionyl chloride: Benzenepropanoyl chloride; (645-45-4), **69**, 180

Phenylseleninic acid: Benzeneseleninic acid: (6996-92-5). **67**, 157

Phenylsulfenyl chloride: Benzenesulfenyl chloride; (931-59-9), **68**, 8

trans-3-(Phenylsulfonyl)-4-(chloromercuri)cyclohexene: Mercury,
chloro[2-(phenylsulfonyl)-3-cyclohexen-1-yl]-, trans-; (102815-53-2), **68**, 148

2-(PHENYLSULFONYL)-1,3-CYCLOHEXADIENE: Benzene, (1,5-cyclohexadien-
1-ylsulfonyl)-; (102860-22-0), **68**, 148

(±)-trans-2-(PHENYLSULFONYL)-3-PHENYLOXAZIRIDINE, **66**, 203, 204

(PHENYLTHIO)NITROMETHANE: Benzene, [(nitromethyl)thio]-; (60595-16-6), **68**, 8

1-Phenyl-1-trimethylsiloxyethylene: Silane, trimethyl [(1-phenylvinyl)oxy]-;
Silane, trimethyl[(1-phenylethenyl)oxy]-; (13735-81-4), **65**, 6

Phosphine, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (R)- or (S)-], **67**, 20, 33

Phosphine, 1,4-butanediylbis[diphenyl-; (7688-25-7), **68**, 64

Phosphine, tetramethylenebis[diphenyl-; (7688-25-7), **68**, 64

Phosphine oxide, [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-, (±)-, (S)-, and
(R)-], **67**, 20

Phosphinic chloride, diphenyl-, **67**, 20

Phosphonate synthesis, **66**, 194

Phosphonic acid, (aminomethyl), diethyl ester, **65**, 119

Phosphonic acid, (diazomethyl)-, dimethyl ester, **65**, 119

Phosphonic acid, diethyl ester; (762-04-9), **66**, 202

Phosphonic acid, [(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]-,
diethyl ester, **65**, 119

Phosphonic acid, [(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl]-, diethyl
ester; (81956-28-7), **66**, 22

Phosphonic acid, (isocyanomethyl)-, diethyl ester, **65**, 119

PHOSPHONIC ACID [[[PHENYLMETHYLENE)AMINO]METHYL]-, DIETHYL ESTER,
65, 119

Phosphonic acid, (phthalimidomethyl)-, diethyl ester, **65**, 119
 Phosphorazidic acid, diphenyl ester; (26386-88-9), **68**, 1
 Phosphoric triamide, hexamethyl-; (680-31-9), **66**, 51, 94
 Phosphorodichloridic acid, 2-chloroethyl ester, **65**, 68
 Phosphorous acid, triethyl ester, **65**, 108. 119
 Phosphorus oxychloride, **66**, 173, 176; **67**, 1; **68**, 41, 162
 Phosphorus tribromide; (7789-60-8), **67**, 210
 Phthalimide, N-(bromoethyl)-, **65**, 119
 Phthalimide, N-(hydroxymethyl)-, **65**, 119
 Pig liver esterase, **69**, 20
 Pinacolone: 2-Butanone, 3,3-dimethyl-; (75-97-8), **69**, 114
 PINENE, (-)- α -: 2-PINENE, (1S,5S)-(-)-; BICYCLO[3.1.1]HEPT-2-ENE,
 2,6,6-TRIMETHYL-, (1S)-; (7785-26-4), **65**, 224
 PINENE, (-)- β -: BICYCLO[3.1.1]HEPTANE, 6,6-DIMETHYL-2-METHYLENE-, (1S)-;
 (18172-67-3), **65**, 224
 Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl), (R*,R*)-(\pm)-;
 (99114-36-0), **69**, 43
 Piperidine, 1-methyl, **67**, 69
 Piperidine, 2,2,6,6-tetramethyl-, **67**, 76
 Piperidine, 1-propanoyl: Piperidine, 1-(1-oxopropyl)-; (14045-28-4), **69**, 44
 Poly(oxy-1,2-ethanediyl), α -[4-(1,1,3,3-tetramethylbutyl)phenyl]- ω -hydroxy-;
 (9002-93-1), **68**, 56
 Poly(oxymethylene), **65**, 215; **68**, 188
 Polyphosphoric acid; (8017-16-1), **69**, 175, 177
 Potassium 3-aminopropylamide (KAPA), **65**, 224
 Potassium bromide, **69**, 212
 Potassium tert-butoxide, **66**, 127, 128, 195; **67**, 125

Potassium fluoride, **69**, 10, 97

Potassium hydride; (7693-26-7), **65**, 224

Potassium hydrogen carbonate, **69**, 97

Potassium hydroxide, **66**, 89

Potassium iodide, **69**, 212

Potassium peroxymonosulfate; (37222-66-5), **69**, 160, 229

Prenyl bromide. **66**, 76

Proline, D-; (344-25-2), **65**, 173

Proline, L-; (147-85-3), **65**, 173

Propanal; (123-38-6). **68**, 64

2-Propanamine, N-ethyl-N-(1-methylethyl)-; (7087-68-5), **68**, 162

2-Propanamine, N-(1-methylethyl)-, **65**, 98

Propane, 1-bromo-3-chloro-2,2-dimethoxy-. **65**, 32

Propane, 2,2'-[(1-chloro-1,2-ethenediyl)bis(oxy)]bis[2-methyl-, (E)-, **65**, 68

Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy)]bis(oxy)bis[2-methyl-,
(R*,R*)-(±)-, **65**, 68

Propane, 2,2'-[(1,2-dichloro-1,2-ethanediy)]bis(oxy)]bis[2-methyl-,
(R*,S*)-, **65**, 68

PROPANE, 2,2'-[1,2-ETHYNYDIYLBIS(OXY)]BIS[2-METHYL-, **65**, 68

1,3-Propanediamine; (109-76-2), **65**, 224; **66**, 131

Propanedinitrile, (phenylmethylene)-, **65**, 32

PROPANEDIOIC ACID, [4-(ACETYLOXY)-2-CYCLOHEXEN-1-YL]-, DIMETHYL
ESTER, cis; (82736-52-5), **69**, 38

PROPANEDIOIC ACID, [4-(ACETYLOXY)-2-CYCLOHEXEN-1-YL]-, DIMETHYL
ESTER, trans; (82736-53-6). **69**, 38

Propanedioic acid, (cyclopropylcarbonyl)-, diethyl ester;
(7394-16-3), **66**, 179

Propanedioic acid, diethyl ester; (105-53-3), **66**, 179
 Propanedioic acid, (methoxymethylene)-, dimethyl ester, **65**, 98
 Propanedioic acid, (3-methyl-2-butenyl)-, dimethyl ester;
 (43219-18-7), **66**, 85
 1,3-Propanediol; (504-63-2), **65**, 32
 1,3-Propanedithiol; (109-80-8), **65**, 150
 2-Propanethiol, 2-methyl-; (75-66-1), **66**, 114
 Propanoic acid, 2-chloro-, (S)-; (29617-66-1), **66**, 159, 172
 PROPANOIC ACID, 3,3-DIETHOXY-, ETHYL ESTER; (10601-80-6), **69**, 238
 Propanoic acid, 2-hydroxy-2-methyl-, methyl ester; (2110-78-3), **66**, 114
 1-Propanol, 2-amino-3-phenyl-, L- or (S)-(-)-; (3182-95-4), **68**, 77
 1-Propanol, 2-chloro-, (S)-(+)-; (19210-21-0), **66**, 172
 2-Propanol, titanium (4+) salt, **65**, 230; **67**, 180; **68**, 49
 2-Propanone, 1-bromo-3-chloro-, dimethyl acetal, **65**, 32
 Propanoyl chloride; (79-03-8), **68**, 83
 Propargyl alcohol: 2-Propyn-1-ol; (107-19-7), **67**, 193
 Propargyl bromide; (160-96-7), **66**, 77, 79, 86
 PROPARGYL CHLORIDE: PROPYNE, 3-CHLORO-; 1-PROPYNE, 3-CHLORO-;
 (624-65-7), **65**, 47
 1-Propen-1-amine, 1-chloro-N,N,2-trimethyl-; (26189-59-3), **66**, 120
 1-Propen-1-amine, 2-phenyl-N-(phenylmethylene)-, **65**, 119
 2-Propenenitrile, **65**, 236
 2-Propenoic acid, 2-(bromomethyl)-, ethyl ester; (17435-72-2), **66**, 224
 2-Propenoic acid, 2-(hydroxymethyl)-, ethyl ester; (10029-04-6), **66**, 224
 2-Propenoic acid, 3-phenyl-, methyl ester: (103-26-4). **68**, 155
 2-PROPENOIC ACID, 3-(PHENYLSULFONYL)-, METHYL ESTER, (Z);
 (91077-67-7), **69**, 169

2-Propen-1-ol; (107-18-6), **66**, 21

2-Propen-1-ol, 1-(trimethylsilyl)-; (95061-68-0), **66**, 21

2-Propenoyl chloride, 2-methyl-, **67**, 98

2-(1-PROPENYL)CYCLOBUTANONE, (E)-: CYCLOBUTANONE, 2-(1-PROPENYL)-, (E)-; (63049-06-9), **67**, 210

Propionaldehyde; (123-38-6), **68**, 64

Propionitrile, 2,2'-azobis[2-methyl-, **67**, 86

Propionyl chloride; (79-03-8), **68**, 83

8-PROPIONYL-(E)-5-NONENOLIDE: 2H-OXECIN-2-ONE, 3,4,5,8,9,10-HEXAHYDRO-9-(1-OXOPROPYL)-, (E)-; (114633-68-0), **69**, 188

2-PROPYL-1-AZACYCLOHEPTANE; (85028-29-1), **66**, 186-188, 193

2-PROPYL-1-AZACYCLOHEPTANE FROM CYCLOHEXANONE OXIME, **66**, 185

Propylene oxide, (R)-(+)-; (15448-47-2), **66**, 172

Propyne, 3-bromo-, (106-96-7), **66**, 86

1-PROPYNE, 3-CHLORO-, **65**, 47

2-Propyn-1-ol, **67**, 193

silylation of, **66**, 3

2-Propyn-1-ol, 3-(trimethylsilyl)-; (5272-36-6), **66**, 7

Protodestannylation, **66**, 77, 78, 80

PULEGONE, (+): p-MENTH-4-(8)-EN-3-ONE, (R)-(+)-; CYCLOHEXANONE, 5-METHYL-2-(1-METHYLETHYLIDENE)-, (R)-; (69-82-7), **65**, 203, 215; **69**, 34

4-Pyridinamine, N,N-dimethyl-, **65**, 12; **68**, 83, 210

Pyridine, **66**, 180, 182; **69**, 130, 240

3-Pyridinecarboxylic acid, methyl ester; (93-60-7), **68**, 155

Pyridine, 4-(dimethylamino)-, **65**, 12; **68**, 83, 210

Pyridine, hydrofluoride, **67**, 86

Pyridinium poly(hydrogen fluoride): Pyridine, hydrofluoride; (32001-55-1),
67, 86

2-Pyridyl triflate, **69, 134**

2(1H)-Pyrimidone, tetrahydro-1,3-dimethyl-; (7226-23-5), **66, 94; 69, 49**

Pyrocatechol; (120-80-9), **66, 184**

Pyrophosphoric acid, disodium salt; (7758-16-9), **66, 219**

1 H-Pyrrole-2,5-dione, 1-phenyl-, **67, 133**

1-Pyrrolidinamine, N-(1-ethyl-2-methylpentylidene)-2-methoxymethyl)-,
 [S-[R⁺,R⁺-(Z)]-], **65, 183**

1-Pyrrolidinamine, N-(1-ethylpropylidene)-2-(methoxymethyl)-, (S)-, **65, 183**

1-Pyrrolidinamine, 2-(methoxymethyl)-, (R)-(+)-; (72748-99-3), **65, 173**

1-Pyrrolidinamine, 2-(methoxymethyl)-, (S)-(-)-; (59983 30 0), **65, 173, 183**

Pyrrolidine, 2-(methoxymethyl)-, (S)-(+)-; (63126-47-6), **65, 173**

Pyrrolidine, 2-(methoxymethyl)-1-nitroso-, (S)-, **65, 183**

1 Pyrrolidinecarboxaldehyde, 2-(hydroxymethyl)-, (S)-(-)-; (55456-46-7),
65, 173

1-Pyrrolidinecarboxaldehyde, 2-(methoxymethyl)-, (S)-(-)-; (63126-45-4),
65, 173

2,5-PYRROLIDINEDIONE, 1-BROMO-, **65, 243**

2-Pyrrolidinemethanol, (S)-(+)-; (23356-96-9), **65, 173**

2-Pyrrolidinone, 1-vinyl-; (88-12-0), **66, 149**

Pyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione, tetrahydro-2-phenyl-5-(phenylmethyl)-
 cis-, **67, 133**

Quinoline; (91-22-5), **68, 182**

RADICAL CYCLIZATION, 66, 75

Ramberg-Bäcklund reaction, 65, 90

**RAMP: (R)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine,
2-(methoxymethyl)-, (R)-; 65, 173, 183**

Red-Al; (22722-98-1), 69, 58

REDUCTION, OF CARBOXYLIC ACIDS TO ALDEHYDES, 66, 121

enantioselective with yeast, 68, 56

vinyl triflate to alkene, 68, 109

REDUCTIVE ANNULATION OF VINYL SULFONES, 67, 163

Rhodium(1+), [(2,3,5,6-)-bicyclo[2.2.1]hepta-2,5-diene][1,4-butanediylbis[diphenylphosphine]-P,P']-, trifluoromethanesulfonate, 68, 64

**Rhodium, [(2,3,5,6-)-bicyclo[2.2.1]hepta-2,5-diene] (2,4-pentanedionate-0,0')-;
(32354-50-0), 68, 64**

**Rhodium(1+), [[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine]-P,P']-
[(1,2,5,6-η)-1,5-cyclooctadiene]-, stereoisomer, perchlorate, 67, 33**

Rhodium diacetate dimer: Acetic acid, rhodium(2+) salt; (5503-41-3), 69, 181

Rhodium, di-μ-chlorobis[(1,2,5,6-η)-1,5-cyclooctadien]di-, 67, 33

Rhodium, (2,5-norbornadiene) (2,4-pentanedionato)-; (32354-50-0), 68, 64

Rhodium on carbon, 67, 187

RING EXPANSION, 65, 17

of cyclic ketoximes, 66, 189

Ruthenium(III) chloride hydrate: Ruthenium chloride, hydrate; (14898-67-0), 68, 41

SALSOLIDINE, (-)-: ISOQUINOLINE, 1,2,3,4-TETRAHYDRO-6,7-

DIMETHOXY-1-METHYL-, (S)- (493-48-1), 67, 60

**SAMP: (S)-1-Amino-2-methoxymethylpyrrolidine: 1-Pyrrolidinamine,
2-(methoxymethyl)-, (S)-; (59983-39-0), 65, 173, 183**

SELENOSULFONATION, 67, 157

Semihydrogenation, 68, 182

Silanamine, N,N-diethyl-1,1,1-trimethyl-; (996-50-9), 60, 83

Silane, acetyltrimethyl-; (13411-48-8), 68, 25

SILANE, 1,3-BUTADIYNE-1,4-DIYLBIS[TRIMETHYL-, 65, 52

Silane, chloromethyldiphenyl-, 67, 125

Silane, chloromethyltrimethyl-, 67, 133; 68, 1

Silane, (3-chloropropyl)trimethyl-; (2344-83-4), 66, 94

Silane, chlorotrimethyl-, 65, 1, 6, 61; 66, 6, 14, 16, 21, 44, 47; 68, 25

Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl-, 65, 17

Silane, (1-cyclobuten-1,2-ylenedioxy)bis[trimethyl-, 65, 17

Silane, (1-cyclohexen-1-yloxy)trimethyl-, 67, 141

SILANE, (DIAZOMETHYL)TRIMETHYL-; (18107-18-1), 68, 1

Silane, [(1-ethoxycyclopropyl)oxy]trimethyl-; (27374-25-0), 66, 51; 67, 210

Silane, ethynyltrimethyl-, 65, 52, 61

Silane, (3-iodopropyl)trimethyl-; (18135-48-3), 65, 94

SILANE, (ISOPROPENYLOXY)TRIMETHYL-, 65, 1

Silane, [(3-methoxy-1-methylene-2-propenyl)trimethyl-, 67, 163

Silane, trichloro-, 67, 20

SILANE, TRIMETHYL (2-METHYLENE-4-PHENYL-3-BUTENYL), 69, 89

SILANE, TRIMETHYL[(1-METHYLETHENYL)OXY]-, 65, 1

Silane, trimethyl[[[4-methylphenyl)sulfonyl]ethynyl]-, 67, 149

Silane, trimethyl (1-methyl-1,2-propadienyl)-; (74542-82-8), 66, 7, 13

SILANE, TRIMETHYL(1-OXO-2-PROPENYL)-; (51023-60-0), 66, 14, 21

Silane, trimethyl[(1-phenylethyl)oxy]-, 65, 6, 12

Silane, trimethyl[(1-phenylvinyl)oxy]-, 65, 6, 12

Silver nitrate, **66**, 111

 reaction with 1-trimethylsilyl-1-butene, **66**, 4

Silver(I) oxide; (20667-12-3), **66**, 111, 115

Silver perchlorate: Perchloric acid, silver(1+) salt, monohydrate;
 (14202-05-8), **67**, 33

Silver(I) trifluoroacetate; (2966-50-9), **66**, 115
 preparation, **66**, 111

Silylamine, N,N-diethyl-1,1,1-trimethyl-; (996-50-9), **68**, 83

Silylation, of 1-alkyne, **68**, 182

Skattebøl rearrangement, **68**, 220

Sodium; (7440-23-5), **66**, 76, 85, 96; **69**, 174

Sodium amalgam, **66**, 96

Sodium benzenesulfinate: Benzenesulfinic acid, sodium salt; (873-55-2),
 68, 148; **69**, 169

Sodium bis(2-methoxyethoxy)aluminum hydride: Aluminate (1-), dihydrobis-
 (2-methoxyethanalato)-, sodium; (22722-98-1), **67**, 13

Sodium bisulfite; (7631-90-5), **68**, 162

Sodium cyclopentadienide, **68**, 198

Sodium dicarbonyl(cyclopentadienyl)ferrate; (12152-20-4), **66**, 96, 107

Sodium dimethyl malonate, **69**, 39, 40

Sodium ethoxide, **67**, 170

Sodium fluoride, aqueous, work-up for organoaluminum reaction, **66**, 188

Sodium hydride; (7646-69-7), **66**, 30, 32, 76, 79, 85, 109, 111, 114; **68**, 92, 198;
 69, 83

Sodium hypochlorite, **69**, 212

Sodium iodide, **66**, 87; **68**, 227

Sodium methoxide, **66**, 76

Sodium naphthalenide, **65**, 166

Sodium nitrite, **66**, 151

Sodium nitromethylate: Methane, nitro-, ion(1-), sodium; (25854-38-0), **68**, 8

Sodium periodate: Periodic acid, sodium salt; (7790-28-5), **68**, 41

Sodium thiosulfate, **69**, 212

Sodium triflate, **69**, 130, 132

Sodium trifluoromethanesulfonate, **69**, 132

Sodium tungstate dihydrate: Tungstic acid, disodium salt, dihydrate;
(10213-10-2), **65**, 166

Sonication, **67**, 133
for reaction of 1,3-diaminopropane with alkali metals, **66**, 130

SPIRO[4.5]DECAN-1,4-DIONE; (39984-92-4), **65**, 17

Stannane, allyltributyl-, (24850-33-7), **68**, 104

Stannane, 1,2-ethenediylbis[dibutyl-, (E)-, **67**, 86

Stannane, ethenyltrimethyl-, (754-06-3), **68**, 116

Stannane, tetrachloro-, **65**, 17

Stannane, tributyl-, **65**, 236

Stannane, tributylchloro-, **67**, 86

Stannane, tributylethynyl, **67**, 86

Stannane, tributyl-2-propenyl-, (24850-33-7), **68**, 104

Stannane, vinylenebis[tributyl-, (E)-, **67**, 86

STETTER REACTION, **65**, 26

Succinic anhydride, **67**, 76

SUCCINIMIDE, N-BROMO-, **65**, 243

Sucrose; α -D-Glucopyranoside, β -D-fructofuranosyl; (57-50-1), **68**, 56

Sulfenylation, with phenylsulfenyl chloride, **68**, 8

Sulfide, methyl p-tolyl; (623-13-2), **68**, 49

Sulfone, ethynyl p-tolyl, **67**, 149
 Sulfonylation, of 1,3-diene, **68**, 148
 2-Sulfonyloxaziridines, preparation, **66**, 207, 208
 Sulfosalicylic acid spray for tlc plates, **66**, 216
 Sulfoxide, enantioselective synthesis, from sulfide, **68**, 49
 Sulfur chloride, **65**, 159
 Sulfur dichloride: Sulfur chloride; (10545-99-0), **66**, 159
 Sulfur diimide, dicarboxy-, dimethyl ester, **65**, 159
 Sulfuryl chloride; (7791-25-5), **68**, 8
 Sulfuryl chloride isocyanate, **65**, 135
 Swern oxidation, **66**, 15, 18

 L-Tartaric acid: (87-69-4), **68**, 92
 Tartaric acid, dibenzoate, (-)- and (+)-, **67**, 20
 Tebbe reagent, **69**, 72
 1,3,4,6-TETRA-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSE: α -D-ARABINO-
 HEXOPYRANOSE, 2-DEOXY-, TETRAACETATE; (16750-06-4), **69**, 66
 2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide; (572-09-8), **69**, 66
 2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide: Glucopyranosyl bromide
 tetraacetate, α -D-; α -D-glucopyranosyl bromide, 2,3,4,6-tetraacetate;
 (572-09-8), **65**, 236; **69**, 66
 Tetrabutylammonium fluoride; (429-41-4), **66**, 110, 111, 115; **69**, 10
 Tetrabutylammonium hydrogen sulfate, **69**, 169
 Tetrabutylammonium hydroxide; (2052-49-5), **66**, 214, 219
 Tetrabutylammonium iodide; (311-28-4), **69**, 83
 Tetrachlorocyclopropene; (6262-42-6), **69**, 144
 Tetrachloroethylene, **69**, 144

Tetrafluoroboric acid, **67**, 210

Tetrafluoroboric acid-diethyl ether complex; (67969-82-8),

66, 97, 98, 100, 107

Tetrafluoroboric acid-dimethyl etherate: Borate(1-), tetrafluoro-, hydrogen,
compound with oxybis[methane] (1:1); (67969-83-9), **67**, 141

1,2,5,6-Tetrahydropyridine synthesis, via immonium ion-vinylsilane cyclization,

68, 188

Tetraisopropyl titanate: Isopropyl alcohol, titanium (4+) salt;

2-Propanol, titanium (4+) salt; (546-68-9), **65**, 230; **67**, 180

Tetrakis(acetonitrile)palladium tetrafluoroborate; (21797-13-7), **66**, 52, 54, 59

Tetrakis(triphenylphosphine)palladium; (14221-01-3), **66**, 61, 62, 66, 68, 69, 74

67, 86, 98, 105, 114; **68**, 116

4,5,4',5'-TETRAMETHOXY-1,1'-BIPHENYL-2,2'-DICARBOXALDEHYDE;

[1,1'-BIPHENYL]-2,2'-DICARBOXALDEHYDE, 4,4',5,5'-TETRAMETHOXY-;

(29237-14-7). **65**, 108

Tetramethylethylenediamine: Ethylenediamine, N,N,N',N'-tetramethyl-;

1,2-Ethanediamine, N,N,N',N'-tetramethyl-; (110-18-9), **68**, 32

2,2,6,6-Tetramethylpiperidine: Piperidine, 2,2,6,6-tetramethyl-; (768-66-1),

67, 76

2,2,6,6-Tetramethylpiperidin-1-oxyl: 1-Piperidinyloxy, 2,2,6,6-tetramethyl-;

(2564-83-2), **69**, 212

Tetramethyltin, **66**, 65

2,5,7,10-Tetraoxabicyclo[4.4.0]decane, cis-: p-Dioxino[2,3,-b]-p-dioxin,

hexahydro-; [1,4]-Dioxino[2,3-b]-1,4-dioxin, hexahydro;

(4362-05-4), **65**, 68

1,4,8,11-TETRATHIACYCLOTETRADECANE; (24194-61-4), **65**, 150

Tetravinyltin, **66**, 53, 55

Tetrionic acids, **66**, 111, 112
 Thiophene; (110-02-1), **69**, 80
 Thiophenol: Benzenethiol; (108-98-5), **68**, 8
 Thiourea: Urea, thio-; (62-56-6), **65**, 150
 Tin chloride, **65**, 17
 Tin tetrachloride: Tin chloride; Stannane, tetrachloro-; (7646-78-8), **65**, 17
 Titanium(IV) isopropoxide: Isopropyl alcohol, titanium(4+) salt: 2-Propanol, titanium(4+) salt; (546-68-9), **65**, 230; **67**, 180; **68**, 49
 Titanium, triisopropoxymethyl-, **67**, 180
 Titanocene dichloride: Titanium, dichloro- π -cyclopentadienyl-; (1271-19-8), **69**, 72, 106
 Tin, tetramethyl-, **66**, 55
 Tin, tetravinyl-, **65**, 53, 55
 Titanium chloride, **65**, 81, 6
 Titanium tetrachloride: Titanium chloride; (7550-45-0), **65**, 81, 6; **66**, 8, 9
 Toluene, *o*-iodo ; (615-37-2), **66**, 74
p-Toluenesulfonic acid, monohydrate; (6192-52-5), **68**; 92, 188
p-Toluenesulfonyl chloride; Benzenesulfonyl chloride, 4-methyl-; (98-59-9), **68**, 188
 α -Toluenethiol, **65**, 215
o-Toluidine, 3-nitro-, **65**, 146
o-Tolyl lithium, preparation, **66**, 69
p-Tolyl 2-(trimethylsilyl)ethynyl sulfone: Silane, trimethyl[(4-methylphenyl)sulfonyl]ethynyl-; (34452-56-7), **67**, 149
o-Tolylzinc chloride; (84109-17-1), **66**, 67, 74
 Transannular cyclization of 1,5-cyclooctadiene, **68**, 175
 Transesterification, **65**, 230; **68**, 155

Transmetallation, of allylmagnesium bromide with bis(tributyltin)oxide, **68**, 104
 of trimethylvinyltin with palladium(0), **68**, 116
 1,2,4-Triazine-3,5,6-tricarboxylic acid, triethyl ester; (74476-38-3), **66**, 149
 1,2,4-Triazines, as Diels-Alder dienes, **66**, 147, 148
 Tribromomethane; (75-25-2), **68**, 220
 Tributylamine; (102-82-9), **66**, 173, 176; **68**, 138
 Tributylstannane; (688-73-3), **65**, 236; **66**, 77, 79, 86; **69**, 66, 188
 Tributylethynylstannane: Stannane, tributylethynyl-; (994-89-8), **67**, 86
 (Z)-3-Tributylstannylmethylene-4-isopropyl-1,1-cyclopentanedicarboxylic acid,
 dimethyl ester, **66**, 77
 Tributyltin chloride: Stannane, tributylchloro-; (1461-22-9), **67**, 86
 Tributyltin hydride: Stannane, tributyl-; (688-73-3), **65**, 236; **66**, 77, 79, 86;
69, 66, 188
 Tributyltinlithium, **69**, 188, 189
 2,3,6-Tricarboethoxypyridine, **66**, 145
 Trichloroacetyl chloride: Acetyl chloride, trichloro-; (76-02-8), **68**, 32, 41; **69**, 238
 1,1,1-Trichloro-4-ethoxy-3-buten-2-one; (83124-74-7), **69**, 238
 Trichlorosilane: Silane, trichloro-; (10025-78-2), **67**, 20
 Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl; (119986-99-1), **69**, 173
 Triethylamine, **66**, 15, 16, 174, 176, 185
 Triethyl orthoacetate; (78-39-7), **66**, 22, 23, 28
 Triethyl orthoformate: Orthoformic acid, triethyl ester; Ethane,
 1,1',1"-[methylidynetris(oxy)]tris-; (122-51-0), **65**, 146
 Triethyl phosphite: Phosphorous acid, triethyl ester; (122-52-1), **65**, 119, 108
 Triethyl phosphonoacetate; (867-13-0), **66**, 220, 224
 TRIETHYL 1,2,4-TRIAZINE-3,5,6-TRICARBOXYLATE; (74476-38-3),
66, 142, 144, 145, 149

Trifluoroacetic acid: (76-05-1), **66**, 111, 115, 136

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride; (407-25-0),
65, 12; **66**, 153

[I,I-BIS(TRIFLUOROACETOXY)]IODOBENZENE, **66**, 132, 134, 136, 141

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride;
(358-23-6), **68**, 116, 138; **69**, 200

Trimethylaluminum: Aluminum, trimethyl-; (75-24-1), **69**, 72

Trimethylamine, **66**, 29, 32

Trimethylamine, 1,1-dimethoxy-, **67**, 52

Trimethyl 2-chloro-2-cyclopropylidenethanoate: Cyclopropane, (1-chloro-2,2,2-trimethoxyethylidene)-; (82979-34-8), **69**, 148

2,2,6-Trimethyl-1,3-dioxen-4-one; (5394-63-8), **66**, 195, 196, 202

3,4,5-Trimethyl-2,5-heptadien-4-ol: 1,5-Heptadien-4-ol, 3,4,5-trimethyl-;
(64417-15-8), **65**, 42

TRIMETHYL (2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE: SILANE,
TRIMETHYL (2-METHYLENE-4-PHENYL-3-BUTENYL)-; (80814-92-2), **69**, 89

Trimethyl ortho-4-bromobutanoate: Butane, 4-bromo-, 1,1,1-trimethoxy-;
(55444-67-2), **67**, 193

Trimethyloxonium tetrafluoroborate: Oxonium, trimethyl-, tetrafluoroborate
(1-); (420-37-1), **65**, 140

1-Trimethylsiloxy-cyclohexene: Silane, (1-cyclohexen-1-yloxy)trimethyl-;
(6651-36-1), **67**, 141

1-Trimethylsiloxy-1-ethoxycyclopropane, **66**, 44

TRIMETHYLSILYLACETYLENE: SILANE, ETHYNYLTRIMETHYL-;
(1066-54-2), **65**, 52, 61

(Z)-4-(TRIMETHYLSILYL)-3-BUTEN-1-OL: 3-Buten-1-ol, 4-(trimethylsilyl)-, (Z)-;
(7682-77-7), **68**, 182, 188

(Z)-4-(Trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate: 3-Buten-1-ol, 4-(trimethylsilyl)-, 4-methylbenzenesulfonate, (Z)-; (87682-62-0), **68**, 188

4-(Trimethylsilyl)-3-butyn-1-ol: 3-Butyn-1-ol, 4-(trimethylsilyl)-; (2117-12-6), **68**, 182

TRIMETHYLSILYLDIAZOMETHANE: Silane, (diazomethyl)trimethyl-; (18107-18-1), **68**, 1

Trimethylsilylmethylmagnesium chloride: Magnesium, [chloro[(trimethylsilyl)-methyl]-; (13170-43-9), **69**, 89

3-Trimethylsilyl-2-propyn-1-ol, **66**, 1, 3

3-Trimethylsilyl-2-propyn-1-yl methanesulfonate, **66**, 2

Trimethylsilyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, trimethylsilyl ester; (27607-77-8), **68**, 64

Trimethyltin chloride: Stannane, chlorotrimethyl-; (1066-45-1), **68**, 116

Trimethylvinyltin: Stannane, trimethylvinyl-; (754-06-3), **68**, 116

Triphenylphosphine: Phosphine, triphenyl-; (603-35-0), **68**, 130, 138; **69**, 39

Tripropylaluminum; (102-67-0), **66**, 186, 188, 193

Tris(diethylamino)sulfonium difluorotrimethylsilicate: Sulfur (1+), tris(N-ethylethanaminato)-, difluorotrimethylsilicate (1-); (59201-86-4), **69**, 48, 49

Tris(tetrabutylammonium) hydrogen pyrophosphate trihydrate; (76947-02-9), **66**, 212, 219

Trithiane, sym-: S-Trithiane; 1,3,5-Trithiane; (291-21-4), **65**, 90

Triton B: Ammonium, benzytrimethyl-, hydroxide; Benzenemethanaminium, N,N,N-trimethyl-, hydroxide; (100-85-6), **68**, 56

Triton X-100: Glycols, polyethylene, mono[p-(1,1,3,3-tetramethylbutyl)-phenyl]ether; Poly(oxy-1,2-ethanediy), α -[4-(1,1,3,3-tetramethylbutyl)-phenyl]- ω -hydroxy-; (9002-93-1), **68**, 56

Tungstic acid, disodium salt, dihydrate, **65**, 166

ULLMANN REACTION, **65**, 108

5,9-UNDECADIEN-1-YNE, 6,10-DIMETHYL-, (E); (22850-55-1), **69**, 120

2,5-Undecanedione; (7018-92-0), **65**, 26

2-Undecene, 2-methyl-, **67**, 125

Urea, thio-, **65**, 150

(S)-Valine, **66**, 153

Valinol: 1-Butanol, 2-amino-3-methyl-, (S)-; (2026-48-4), **67**, 52

Vibro-mixer, **65**, 52

Vilsmeier-Haack reagent, **66**, 121

Vinyl acetate: Acetic acid vinyl ester; Acetic acid ethenyl ester; (108-05-4), **65**, 135

VINYLATION OF ENOLATES, **66**, 95, 104

Vinyl bromide (593-60-2), **68**, 109

VINYL CATION EQUIVALENT, **66**, 95

Vinyl cation synthons, **66**, 102

Vinyl lithium; (917-57-1), **66**, 53, 55; **69**, 81

Vinylmagnesium bromide, (1826-67-1), **68**, 109

N-Vinyl-2-pyrrolidone; (88-12-0), **66**, 145, 146, 149

Vinyl radical cyclization, **66**, 81, 82

Vinylsilane, cyclization with imminium ion, **68**, 188

Vinyl triflate, synthesis, **68**, 116, 138

Volatile reaction products, apparatus for collecting, **66**, 161, 162

Wittig rearrangement, **66**, 19

Yeast, baker's, **68**, 49

Zinc; (7440-66-6), **68**, 32

Zinc chloride; (7646-85-7), **66**, 43, 45, 51, 61, 62, 68, 69

Zinc, chloro(2-methylphenyl)-; (84109-17-1), **66**, 74

Zinc-copper couple: Copper, compound with zinc (1:1); (12019027-1),
67, 98; **68**, 32, 41

ZINC HOMOENOLATE, **66**, 43

Zipper reaction, alkyne isomerization, **66**, 129

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General Reference: *Prudent Practices for Disposal of Chemicals from Laboratories*, National Academy Press, Washington, D.C. 1983

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- 3a. Metal salts and other inorganic materials.
- 3b. Organic residues (tars) and other unwanted organic materials.
- 3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or academic setting, provision should be made for dealing with the more environmentally offensive categories.

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgement of an environmentally aware professional.

- 1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.
- 1b. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.
- 2a. All waste solvents and solvent solutions of organic waste.
- 2c. Aqueous waste containing dissolved organic material known to be toxic.
- 2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.
3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases:

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suck-back and on into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10-100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids:

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste

solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic materials should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids:

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note:

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

**If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

PREFACE

In keeping with tradition, Volume 70 contains 31 procedures, carefully checked by independent laboratories, dealing with important compounds of varied nature. For the first time, this volume has added a new section to each procedure—"Waste Disposal Information." This includes any special disposal of chemical waste utilized by the submitters in order to comply with modern, clean disposal practices of toxic materials. If no unusual disposal method was employed, the editor has inserted the following statement, "All toxic materials were disposed of in accordance with *Prudent Practices for Disposal of Chemicals from Laboratories*, National Academy Press; Washington, DC, 1983." This monograph should be consulted by all users of *Organic Syntheses* procedures in keeping with current trends to preserve the environment. A synopsis of the disposal guidelines are included just prior to this preface.

Since protein and peptide syntheses are rapidly falling into the hands of organic chemists, four procedures to reach building blocks are presented first. N-protected α -amino acids in the form of its β -lactone; **N α -(BENZYLOXY-CARBONYL)- β -(PYRAZOL-1-YL)-L-ALANINE** and the preparation of both β -lactones, **N-tert-BUTOXYCARBONYL-L-SERINE- β -LACTONE** and the **p-TOLUENESULFONIC ACID SALT OF (S)-3-AMINO-2-OXETANONE** are described starting from **N-tert-BUTOXYCARBONYL-L-SERINE**. A useful S or R serine derivative, **1,1-DIMETHYLETHYL (S) or (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE** is described followed by the improved preparation of **N-(BENZYLOXY-CARBONYL)-L-VINYLGLYCINE METHYL ESTER**, an important intermediate as well as an important substance in biological processes.

The continued fascination chemists possess with asymmetric synthesis provides the basis for the next four procedures. The synthesis of **(R)-(-)-10-METHYL-1(9)-OCTALONE-2** is a nice demonstration of an asymmetric Michael addition by a chiral imine followed by an aldol—in short an asymmetric Robinson annulation. The asymmetric glycolization to **STILBENE DIOL (R,R-1,2-DIPHENYL-1,2-ETHANEDIOL)** represents an olefin oxidation using catalytic alkaloids in tandem with osmium tetroxide. As reagents for a variety of asymmetric alkylations, the preparation of **2-CYANO-6-PHENYLOXAZOLOPIPERIDINE** is presented as well as another route to

(S)- AND (R)-1,1'-BI-2-NAPHTHOL, obtained by resolution of its pentanoate ester with cholesterol esterase.

In accordance with the editorial board's recent policy reflecting its interest in obtaining more procedures for important heterocyclic compounds, seven procedures for heterocyclic ring syntheses and three of substituent modification follow: **3,4-DIETHYLPYRROLE** and the highly symmetric **OCTA-ETHYLPORPHYRIN** are described making this synthetic porphyrin readily available for biological modeling and inorganic chemical applications.

This is followed by an example of a pyrrole synthesis: **DIMETHYL-3-PHENYLPYRROLE-2,5-DICARBOXYLATE** is obtained via an inverse demand Diels-Alder synthesis using **DIMETHYL-1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE**. A rhodium-catalyzed cyclization of acetylenes with α -diazocarbonyls provides a nice route to **ETHYL 2-METHYL-5-PHENYL-3-FURAN CARBOXYLATE** and related 2,3,5-trisubstituted furans. Two procedures dealing with cyclization to nitrogen heterocycles are included—the first is an example of iodolactamization to give **8-EXO-IODO-2-AZABICYCLO[3.3.0]OCTAN-3-ONE** and the second procedure is a nice demonstration of an alkyne-iminium cyclization furnishing **(E)-1-BENZYL-3-(1-iodoethylidene)PIPERIDINE**. A sulfur heterocycle, **9-THIABICYCLO[3.3.1]NONANE-2,6-DIONE** is also included which has shown to be a versatile intermediate to a number of other sulfur heterocycles. The current interest in cryptands for complexing metal ions provides the rationale for the procedure describing **(TRIAZA-21-CROWN-7)4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE**.

Modification and elaboration of heterocycles are demonstrated by the transformation of dihydroisoquinolines to **7,8-DIMETHOXY-1,3,4,5-TETRAHYDRO 2H,3-BENZAZEPIN-2-ONE**, the conversion of 2-bromopyrrole to **N-tert-BUTOXY-2-TRIMETHYLSILYLPYRROLE**, and substitution of the α -phenylsulfonyl group in pyran to furnish **TETRAHYDRO-2-(PHENYLETHYNYL)-2H-PYRAN**.

The next group of procedures appearing herein reflects a variety of useful new reagents for performing a variety of synthetic tasks. The preparation of **TRIS(TRIMETHYLSILYL)SILANE** as a hydrogen donor source in free radical chemistry is a welcome addition, as is the preparation of **9-BORABICYCLO[3.3.1]NONANE DIMER**, the well recognized hydroboration agent. A stable methylene transfer agent, **IRON (1⁺), DICARBONYL(η^5 -2,4-CYCLOPENTADIEN-1-YL) (DIMETHYLSULFONIUM η -METHYLIDE)-,TETRAFLUOROBORATE(1⁻)** is described and shows its utility in the synthesis of **1,1-DIPHENYLCYCLOPROPANE**. The clean

1,2-addition of **RCu(CN)ZnI** reagents to α,β -unsaturated aldehydes is nicely demonstrated as well as the 1,4-addition of **ORGANOBIS(CUPRATES)** in a spiroannellation affording **9,9-DIMETHYLSPIRO[4.5]DECAN-7-ONE**. The interesting properties of **ALKYNYL ARYL IODONIUM SALTS** are highlighted in the preparation of the conjugated enyne, **E-5-PHENYL-DO-DEC-5-EN-7-YNE**.

The last group of procedures included in this volume represent efficient means of reaching important and pivotal intermediates for a host of functionalized materials. The simple, single step, synthesis of **2-METHYL-1,3-CYCLOPENTANEDIONE** from cheap materials is presented, followed by a convenient procedure leading to large scale preparation of the functionalized diene, **(E,Z)-1-METHOXY-2-METHYL-3-(TRIMETHYLSILOXY)-1,3-PENTADIENE**. Another useful diene, generated under nickel catalysis between a 1,3-dithiolane and a Grignard reagent, is **(E,E)-TRIMETHYL(4-PHENYL-1,3-BUTADIENYL)SILANE**. A rapid entry into fluorine-containing alkynes is the procedure describing the pyrolysis of α -**ACYLMETHYLENEPHOSPHORANES** which produces a good yield of **ETHYL 4,4,4-TRIFLUORO-2-BUTYNOATE**. C-Acylation of an enolate using methyl cyanofornate provides a convenient source of the α -carbomethoxyoctalone, **METHYL (1 α ,4A β ,8A α)-2-OXO-DECAHYDRO-1-NAPHTHOATE** and represents a good example of generating β -keto esters under mild conditions. The nitron functionality is featured in a procedure which makes it in a single step from secondary amines and **6-METHYL-2,3,4,5-TETRAHYDROPYRIDINE N-OXIDE** is the example described. Finally, the synthesis of phospholes: **1-PHENYL-2,3,4,5-TETRAMETHYLPHOSPHOLE** is described as an example of the versatility of zirconocene chemistry.

In closing, the editor acknowledges the skills, patience, and dedication of all my colleagues on the Editorial Board of *Organic Syntheses* and their students and coworkers who painstakingly checked all the procedures included in this edition. Furthermore, the guidance, calming effect, and talent of Professor Jeremiah Freeman, Secretary to the Board, in demanding and maintaining the highest standards are truly appreciated. The final, clearly discernable, and attractive product before the reader is due entirely to Dr. Theodora W. Greene, Assistant Editor to *Organic Syntheses*, and the Freeman staff at the University of Notre Dame who typed and prepared the final manuscript.

ALBERT I. MEYERS

Fort Collins, Colorado
May 1991

CONTENTS

Sunil V. Pansare, Gregory Huyer, Lee D. Arnold, and John C. Vederas	1	SYNTHESIS OF N-PROTECTED α -AMINO ACIDS FROM N-(BENZYLOXYCARBONYL)- L-SERINE VIA ITS β -LACTONE: N α -(BENZYLOXYCARBONYL)- β -(PYRAZOL-1-YL)-L-ALANINE
Sunil V. Pansare, Lee D. Arnold, and John C. Vederas	10	SYNTHESIS OF N- <i>tert</i> -BUTOXY- CARBONYL-L-SERINE β -LACTONE AND THE <i>p</i> -TOLUENESULFONIC ACID SALT OF (S)-3-AMINO- 2-OXETANONE
Philip Garner and Jung Min Park	18	1,1-DIMETHYLETHYL (S)- OR (R)- 4-FORMYL-2,2-DIMETHYL- 3-OXAZOLIDINECARBOXYLATE: A USEFUL SERINAL DERIVATIVE
Michael Carrasco, Robert J. Jones, Scott Kamel, H. Rapoport, and Thien Truong	29	N-(BENZYLOXYCARBONYL)-L- VINYLGLYCINE METHYL ESTER
G. Revial and M. Pfau	35	(R)-(-)-10-METHYL-1(9)-OCTAL-2-ONE
Blaine H. McKee, Declan G. Gilheany, and K. Barry Sharpless	47	(R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)
Martine Bonin, David S. Grierson, Jacques Royer, and Henri-Philippe Husson	54	A STABLE CHIRAL 1,4-DIHYDRO- PYRIDINE EQUIVALENT FOR THE ASYMMETRIC SYNTHESIS OF SUBSTITUTED PIPERIDINES: 2-CYANO-6-PHENYLOXAZOLO- PIPERIDINE
Romas J. Kazlauskas	60	(S)-(-)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL
Jonathan L. Sessler, Azadeh Mozaffari, and Martin R. Johnson	68	3,4-DIETHYLPYRROLE AND 2,3,7,8,12,13,17,18-OCTAETHYL- PORPHYRIN
Dale L. Boger, James S. Panek, and Mona Patel	79	PREPARATION AND DIELS-ALDER REACTION OF A REACTIVE, ELECTRON-DEFICIENT HETERO- CYCLIC AZADIENE: DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXY- YLATE. 1,2-DIAZINE AND PYRROLE INTRODUCTION

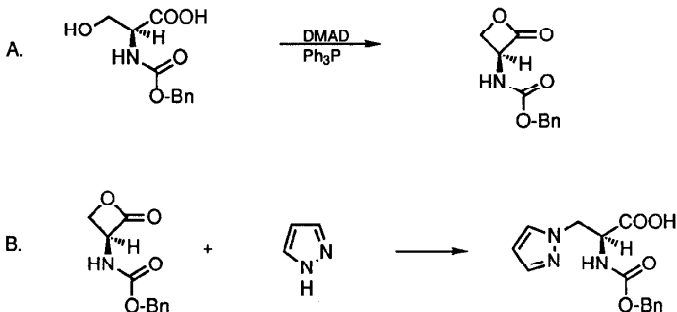
Iluv M. L. Davies, William R. Cantrell, Jr., Karen R. Romines, and Jonathan S. Baum	93	SYNTHESIS OF FURANS VIA RHODIUM(II) ACETATE-CATALYZED REACTION OF ACETYLENES WITH α -DIAZOCARBONYLS: ETHYL 2- METHYL-5-PHENYL-3-FURAN- CARBOXYLATE
Spencer Knapp and Frank S. Gibson	101	IODOLACTAMIZATION: 8- <i>exo</i> -IODO-2- AZABICYCLO[3.3.0]OCTAN-3-ONE
H. Arnold, L. E. Overman, M. J. Sharp and M. C. Witschel	111	(E)-1-BENZYL-3-(1-iodoethylidene)- PIPERIDINE: NUCLEOPHILE- PROMOTED ALKYNE-IMINIUM ION CYCLIZATIONS
Roger Bishop	120	9-THIABICYCLO[3.3.1]NONANE-2,6- DIONE
Krzysztof E. Krakowiak and Jerald S. Bradshaw	129	4-BENZYL-10,19-DIETHYL-4,10,19- TRIAZA-1,7,13,16-TETRAOXACYCLO- HENEICOSANE (TRIAZA-21-CROWN-7)
George R. Lenz and Ralph A. Lessor	139	TETRAHYDRO-3-BENZAZEPIN-2- ONES: LEAD TETRAACETATE OXIDATION OF ISOQUINOLINE ENAMIDES
Wha Chen, E. Kyle Stephenson, Michael P. Cava, and Yvette A. Jackson	151	2-SUBSTITUTED PYRROLES FROM N- <i>tert</i> -BUTOXYCARBONYL- 2-BROMOPYRROLE: N- <i>tert</i> -BUTOXY- 2-TRIMETHYLSILYLPYRROLE
Dearg S. Brown and Steven V. Ley	157	SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC ETHERS: TETRAHYDRO 2-(PHENYLETHYNYL)-2H-PYRAN
Joachim Dickhaut and Bernd Giese	164	TRIS(TRIMETHYLSILYL)SILANE
John A. Soderquist and Alvin Negron	169	9-BORABICYCLO[3.3.1]NONANE DIMER
Matthew N. Mattson, Edward J. O'Connor, and Paul Helquist	177	CYCLOPROPANATION USING AN IRON-CONTAINING METHYLENE TRANSFER REAGENT: 1,1-DIPHENYL- CYCLOPROPANE

Ming Chang P. Yeh, Huai Gu Chen, Paul Knochel	195	1,2-ADDITION OF A FUNCTIONALIZED ZINC-COPPER ORGANOMETALLIC [RCu(CN)ZnI] TO AN α,β - UNSATURATED ALDEHYDE: (E)-2-(4-HYDROXY-6-PHENYL-5- HEXENYL)-1H-ISOINDOLE- 1,3(2H)-DIONE
Paul A. Wender, Alan W. White, and Frank E. McDonald	204	SPIROANNELENATION VIA ORGANOBIS- (CUPRATES): 9,9-DIMETHYLSPIRO- [4.5]DECAN-7-ONE
Peter J. Stang and Tsugio Kitamura	215	ALKYNYL(PHENYL)IODONIUM TOSYLATES: PREPARATION AND STEREOSPECIFIC COUPLING WITH VINYL COPPER REAGENTS. FORMATION OF CONJUGATED ENYNE. 1-HEXYNYL(PHENYL)- IODONIUM TOSYLATE AND (E)-5-PHENYLDODEC-5-EN-7-YNE
Philip G. Meister, Matthew R. Sivik, and Leo A. Paquette	226	2-METHYL-1,3-CYCLOPENTANEDIONE
David C. Myles and Mathew H. Bigham	231	PREPARATION OF (E,Z)-1-METHOXY- 2-METHYL-3-(TRIMETHYLSILOXY)- 1,3-PENTADIENE
Zhi-Jie Ni and Tien-Yau Luh	240	NICKEL-CATALYZED SILYLOLEFIN- ATION OF ALLYLIC DITHIOACETALS: (E,E)-TRIMETHYL(4-PHENYL-1,3- BUTADIENYL)SILANE
B. C. Hamper	246	α -ACETYLENIC ESTERS FROM α - ACYLMETHYLENPHOSPHORANES: α -ETHYL 4,4,4-TRIFLUOROTETROLATE
Simon R. Crabtree, Lewis N. Mander, and S. Paul Sethi	256	SYNTHESIS OF β -KETO ESTERS BY C-ACYLATION OF PREFORMED ENOLATES WITH METHYL CYANOFORMATE: PREPARATION OF METHYL (1 α ,4 α ,8 α)-2-OXO- DECAHYDRO-1-NAPHTHOATE
Shun-ichi Murahashi, Tatsuki Shiota, and Yasushi Imada	265	OXIDATION OF SECONDARY AMINES TO NITRONES: 6-METHYL-2,3,4,5- TETRAHYDROPYRIDINE N-OXIDE
Paul J. Fagan and William A. Nugent	272	1-PHENYL-2,3,4,5-TETRAMETHYL- PHOSPHOLE
Unchecked Procedures	278	

Cumulative Author Index for Volume 70	282
Cumulative Subject Index for Volume 70	284

ORGANIC SYNTHESIS

**SYNTHESIS OF N-PROTECTED α -AMINO ACIDS FROM N-(BENZYLOXYCARBONYL)-L-SERINE VIA ITS β -LACTONE:
N α -(BENZYLOXYCARBONYL)- β -(PYRAZOL-1-YL)-L-ALANINE
(Serine, N-carboxy-, β -lactone, benzyl ester, L-)**



Submitted by Sunil V. Pansare, Gregory Huyer, Lee D. Arnold, and John C. Vederas.¹

Checked by M. Jones, G. L. Olson, and David L. Coffen.

1. Procedure

A. *N*-(Benzyloxycarbonyl)-L-serine β -lactone.² A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, an argon inlet adaptor, a low temperature thermometer, and a rubber septum (Note 1). The flask is charged with tetrahydrofuran (1.1 L) and triphenylphosphine (42.1 g, 160 mmol, Note 2). The triphenylphosphine is dissolved with stirring and the flask is then cooled to -78°C with a dry ice-acetone bath (Note 3). Distilled dimethyl azodicarboxylate (17.7 mL, 160

mmol, $d = 1.33$ g/mL at 25°C) is added dropwise with a syringe over 10 min (*Caution*, Note 4). The resulting pale yellow solution is stirred at -75° to -78°C for 10 min, at which point a milky white slurry is obtained. The rubber septum on the flask is quickly replaced with a 1-L pressure-equalizing dropping funnel containing a solution of N-(benzyloxycarbonyl)-L-serine (38.3 g, 160 mmol) in tetrahydrofuran (240 mL), (Notes 2, 5) which is added dropwise to the mixture over 30 min. After completion of the addition, the mixture is stirred at -75° to -77°C for 20 min, the cooling bath is removed, and the mixture is slowly warmed with stirring to room temperature over 2.5 hr (Note 6). The solvent is removed on a rotary evaporator at 35°C. The residual pale yellow syrup is dried briefly (15 min) under high vacuum (~0.2 mm) and suspended in hexane/ethyl acetate (4/1, 20 mL). Ethyl acetate (30 mL) is added to give a solution which is applied to a 10 x 23-cm column of flash silica gel³ (800 g) packed in hexane/ethyl acetate (4/1). The flask and the sides of the column are rinsed with additional ethyl acetate (20 mL), and this is added to the column which is then eluted with hexane/ethyl acetate (4/1, 2.6 L). The solvent is changed to hexane/ethyl acetate (3/2) and 500-mL fractions are collected. Concentration of fractions 6-10 on a rotary evaporator gives 15.5 g (44%) of analytically pure N-(benzyloxycarbonyl)-L-serine β -lactone (Note 7). Fractions 11-14 contain slightly impure β -lactone. The solid obtained from concentration of these fractions on a rotary evaporator is dissolved in dichloromethane (50 mL) and precipitated by addition of hexane (50 mL) followed by cooling to -20°C (0.5 hr). The process is repeated twice to afford additional β -lactone (1.25 g). The total yield is 16.8 g (47%) (Note 8).

B. N α -(Benzyloxycarbonyl)- β -(pyrazol-1-yl)-L-alanine.^{2,4} A 500-mL, single-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum and an argon inlet (Note 1). The flask is charged with N-(benzyloxycarbonyl)-L-serine β -lactone (15 g, 68 mmol) and anhydrous acetonitrile (240 mL, Note 2). The cloudy mixture is stirred and solid pyrazole (4.9 g, 72 mmol) (Note 9) is added. The

rubber septum is quickly replaced with a reflux condenser and an argon inlet adaptor, and the reaction mixture is heated in an oil bath at 52-54°C for 24 hr. The solvent is removed on a rotary evaporator to leave a white solid that is dried under vacuum for 30 min. Sodium hydroxide (1 N, 69 mL) is added, the suspension is diluted with distilled water (350 mL) and the mixture is stirred vigorously for 5 min. It is then extracted with dichloromethane (3 x 100 mL) to remove unreacted pyrazole and side products. The aqueous phase is cooled in an ice bath to ca. 4°C, and concentrated hydrochloric acid is added with stirring to bring the pH to 1 (about 10 mL required). The resulting precipitate is filtered, washed with water (ca. 75 mL), air dried, and then completely dried in a desiccator over phosphorus oxide (P_2O_5) at 0.2 mm for 12 hr. This material is recrystallized from ethyl acetate (350 mL) to give 7.3 g of pure product (37% yield). Concentration of the mother liquor on a rotary evaporator and recrystallization from the minimum volume of ethyl acetate gives an additional 1.1 g of analytically pure N^α-(benzyloxycarbonyl)-β-(pyrazol-1-yl)-L-alanine. The total yield is 8.4 g (43%) (Note 10).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven, and then assembled and maintained under an atmosphere of dry argon or nitrogen before use. It is essential to complete the purification of the β-lactone as rapidly as possible because this compound is unstable in the crude reaction mixture.

2. Triphenylphosphine (obtained from General Intermediates of Canada) and N-(benzyloxycarbonyl)-L-serine (obtained from Sigma Chemical Company) were dried under reduced pressure over P_2O_5 for 72 hr and 24 hr, respectively. Acetonitrile was refluxed over calcium hydride (CaH_2) for ca. 10 hr and distilled from CaH_2 before

use. Tetrahydrofuran was distilled from sodium benzophenone ketyl directly into the glassware (under argon) the day before and stored under argon overnight until used.

3. The temperature of the solution should be about -75°C before dimethyl azodicarboxylate is added.

4. Dimethyl azodicarboxylate (manufactured by Tokyo Kasei Kogyo Co., Japan) was purchased from CTC Organic, 792 Windsor Street, Atlanta, GA 30315. Overheating of dimethyl azodicarboxylate should be avoided because of the danger of explosion. Distillation should be conducted from a temperature-controlled bath in the hood behind a safety shield. The material used distilled at $71-72^{\circ}\text{C}$ (2 mm), at a bath temperature of $84-86^{\circ}\text{C}$. It is important that the addition of this compound to the reaction mixture be carried out at a constant rate without interruption because it tends to freeze in the syringe needle. The checkers explored the use of diethyl azodicarboxylate because of its lower cost and wider availability. However, the corresponding hydrazine derivative is more difficult to separate from the β -lactone product of this step.

5. The solution of dried N-(benzyloxycarbonyl)-L-serine was made up separately in an addition funnel under an atmosphere of argon. This avoids complications that may arise if the funnel is prefitted on the reaction vessel.

6. The reaction vessel was placed in a water bath at room temperature after the temperature of the mixture was ca. 15°C .

7. The reaction usually works better on a small scale (25 mmol) and a yield of 60% or more is usually obtained. The flash chromatography column was eluted so that the solvent level dropped 1 cm/13 sec. This corresponds to an approximate rate of 362 mL/min. The concentration and purification of the reaction mixture should be carried out as quickly as possible on the same day. Although storage of the concentrated reaction mixture at -20°C overnight results in substantial decomposition

of the β -lactone, column fractions containing pure β -lactone (after chromatography) can be stored at 4°C overnight and concentrated on the following day.

The β -lactone is readily visualized by TLC (Merck, Kieselgel 60 F₂₅₄, 0.25-mm thickness, hexane/ethyl acetate (55/45) as solvent system) under UV, or by using bromocresol green spray (0.04% in EtOH, made blue by NaOH) followed by heating of the plate to detect the β -lactone as a yellow spot on a blue background.

8. The product exhibits the following properties: mp 133-134°C; $[\alpha]_D^{22}$ -26.5° (CH₃CN, c 1); IR cm⁻¹: 3355, 1847, 1828, 1685, 1530, 1268; ¹H NMR (360 MHz, CD₂Cl₂) δ : 4.4 (m, 2 H, CH-CH₂-O), 5.0-5.1 (m, 1 H, N-CH-CO), 5.12 (s, 2 H, OCH₂Ph), 5.5-5.7 (br, s, 1 H, NH), 7.3-7.4 (s, 5 H, ArH); EI-MS: M⁺ 221.0681 (221.0688 calcd for C₁₁H₁₁NO₄). Anal. Calcd for C₁₁H₁₁NO₄: C, 59.71; H, 4.97, 6.33. Found: C, 59.66; H, 4.92; N, 6.32.

The optical purity was determined as previously described,^{2b} and corresponds within experimental error to that of the starting material. N-(Benzyloxycarbonyl)-L-serine obtained from Sigma typically contains 0.75-2.80% of the D-isomer.

9. Pyrazole was obtained from Aldrich Chemical Company, Inc.

10. The reaction usually is more successful on a smaller scale and yields up to 70% can be obtained. The product exhibits the following properties: mp 168-169°C, $[\alpha]_D^{22}$ -53.5°; (DMF, c 1); IR (KBr disc) cm⁻¹: 3350, 1745, 1696, 1534, 1260; ¹H NMR (360 MHz, CD₃OD) δ : 4.4-4.5 (m, 1 H, CH), 4.60-4.70 (m, 2 H, CH₂N), 5.08 (s, 2 H, OCH₂Ph), 6.25 (t, 1 H), 7.3 (s, 5 H, -Ph), 7.48 (d, 1 H), 7.52 (d, 1 H); MS: FAB MS in glycerol m/z 290 (MH⁺, 36%). Anal. Calcd for C₁₄H₁₅N₃O₄: C, 58.13; H, 5.23; N, 14.53. Found: C, 57.86; H, 5.25; N, 14.36.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

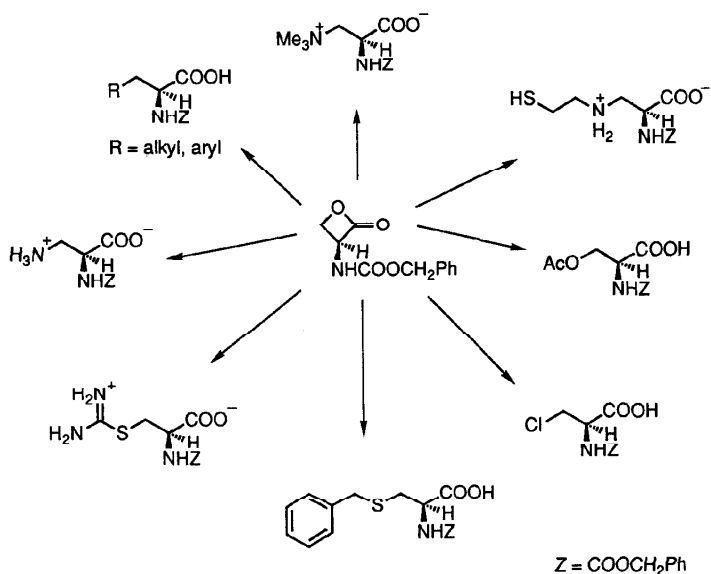
A large number of α -amino acids with interesting biological properties occur in nature.⁵ This fact, together with the utility of amino acids as chiral synthons, catalysts, and auxiliaries,⁶ has stimulated extensive interest in their chemical synthesis.⁷ Serine is an especially attractive starting material for preparation of other amino acids because both enantiomers are commercially available (in both free and various N-protected forms) with high optical purity at relatively low cost. Recent work has shown that chiral N protected serine β -lactones are readily formed under modified Mitsunobu conditions and that they react readily with a variety of carbon, nitrogen, oxygen, sulfur, and halogen nucleophiles to afford optically pure N-protected α -amino acids (Scheme 1).^{2,8}

The procedure given here describes the preparation and use of N-(benzyloxycarbonyl)-L-serine β -lactone for the synthesis of a protected β -substituted alanine, N α -(benzyloxycarbonyl)- β -(pyrazol-1-yl)-L-alanine. This compound occurs in watermelon seeds,⁹ and has been used as a histidine analog.^{4b} Its synthesis illustrates how serine β -lactones can provide convenient access to other β -substituted alanines such as mimosine, willardiine, quisqualic acid, and stizolobic acid which occur in higher plants.^{5a,10} Many previous chemical syntheses of racemic pyrazolylalanine have been published; the best of these routes appear to be from acetamidoacrylic acid (94-96% yield)¹¹ and from O-acetylserine (40-45%).^{4c} The

racemate has been resolved.^{4b} The β -(pyrazol-1-yl)-L-alanine synthase enzyme has been purified and used to make the chiral material from O-acetyl-L-serine.¹²

The crystalline N-(benzyloxycarbonyl)-serine β -lactone is easily handled in air at room temperature and can be stored dry at -20°C for many months without decomposition. Solutions of this compound in non-nucleophilic organic solvents (e.g., chloroform, ethyl acetate) or in neutral or slightly acidic water (pH 3-6) are stable for several days. Aqueous base rapidly hydrolyzes the β -lactone 2b,⁸

Scheme 1



1. Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2.
2. (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105; (b) Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-(Benzyloxycarbonyl)-L-serine: L-Serine, N-[(phenylmethoxy)carbonyl]- (9);
(1145-80-8)

N-(Benzyloxycarbonyl)-L-serine β -lactone: Serine, N-carboxy-, β -lactone, benzyl ester, L- (9); (26054-60-4)

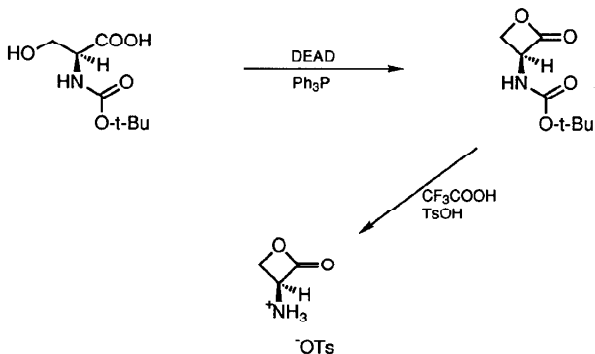
Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Dimethyl azodicarboxylate: Diazenedicarboxylic acid, dimethyl ester (9); (2446-84-6)

N α -(Benzyloxycarbonyl)- β -(pyrazol-1-yl)-L-alanine: 1H-Pyrazole-1-propanoic acid, α -[[(phenylmethoxy)carbonyl]amino]-, (S)- [New compound: No registry number yet]
Pyrazole (8); 1H-Pyrazole (9); (288-13-1)

**SYNTHESIS OF N-tert-BUTOXYCARBONYL-L-SERINE β -LACTONE AND
THE p-TOLUENESULFONIC ACID SALT OF
(S)-3-AMINO-2-OXETANONE**

(Carbamic acid, (2-oxo-3-oxetanyl)- 1,1-dimethylethyl ester, (S)-) and
(2-Oxetanone, 3-amino-, (S)-, 4-methylbenzenesulfonate)



Submitted by Sunil V. Pansare, Lee D. Arnold, and John C. Vederas.¹

Checked by P. S. Manchand, P. Mastrodonato-DeLora, and D. L. Coffen.

1. Procedure

A. N-(tert-Butoxycarbonyl)-L-serine β -lactone.² A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, an argon inlet adaptor, a low temperature thermometer, and a rubber septum (Note 1). The flask is charged with tetrahydrofuran (1.1 L) and triphenylphosphine (42.1 g, 160 mmol) (Note 2). The triphenylphosphine is dissolved with stirring, and the flask is cooled to -78°C with a dry

ice-acetone bath maintained at that temperature (Note 3). Distilled diethyl azodicarboxylate (DEAD) (27.86 g, 160 mmol) is then added dropwise with a syringe over 10 min (Note 4). The resulting pale yellow solution is stirred at -75°C to -78°C for 10 min, at which point a milky slurry is obtained. The rubber septum on the flask is quickly replaced with a 1-L pressure equalizing dropping funnel containing a solution of N-(tert-butoxycarbonyl)-L-serine (32.8 g, 160 mmol) in tetrahydrofuran (240 mL), (Notes 2 and 5) which is then added dropwise to the mixture over 30 min. After completion of the addition, the mixture is stirred at -75°C to -78°C for 20 min, the cooling bath is removed, and the mixture is slowly warmed with stirring to room temperature over 2.5 hr (Note 6). The solvent is removed on a rotary evaporator at 35°C. The residual pale yellow syrup is suspended in hexane/ethyl acetate (85/15, 20 mL), slurried, and the solid is removed by filtration. The filtrate is diluted with ethyl acetate (30 mL) to give a solution which is applied to a 10 x 23-cm column of flash silica gel³ (800 g) packed in hexane/ethyl acetate (85/15). The flask and the sides of the column are rinsed with additional ethyl acetate (20 mL), which is added to the column that is then eluted with hexane/ethyl acetate (85/15, 2.7 L). The solvent is changed to hexane/ethyl acetate (7/3) and 500-mL fractions are collected. Concentration of fractions 6-12 on a rotary evaporator gives 12.07 (40%) of pure N-(tert-butoxycarbonyl)-L-serine β -lactone (Notes 7 and 8).

*B. (S)-3-Amino-2-oxetanone p-toluenesulfonic acid salt.*⁴ A 500-mL, single-necked, round-bottomed flask is equipped with a magnetic stirring bar and an argon inlet adaptor (Note 1). The flask is charged with a mixture of N-(tert-butoxycarbonyl)-L-serine β -lactone (14.0 g, 74.8 mmol) and anhydrous p-toluenesulfonic acid (13.5 g, 78.5 mmol) (Note 9). The argon inlet adaptor is replaced with a rubber septum and an argon inlet and the flask is cooled in an ice bath for ca. 15 min. Anhydrous trifluoroacetic acid (200 mL, Note 10) is added by cannula along the sides of the flask over 20 min (stirring is initiated when possible). The pale yellow solution is stirred at

0°C for 10 min, the trifluoroacetic acid is removed on a rotary evaporator at below 30°C, and the resulting syrup is placed under high vacuum (~ 0.2 mm) for ca. 1 hr. Anhydrous ether (200 mL, Note 11) is added to the resulting solid, the mixture is triturated to break up lumps, and the suspension is filtered. The solid thus obtained is washed with ether (100 mL), air dried (5 min), and then dried under reduced pressure (0.2 mm) overnight to give 10.4 g (95% yield) of (S)-3-amino-2-oxetanone p-toluenesulfonic acid salt (Note 12).

2. Notes

1. The glass components of the apparatus are dried overnight in a 120°C oven, and then assembled and maintained under an atmosphere of dry nitrogen or argon before use.

2. Triphenylphosphine (obtained from Aldrich Chemical Company, Inc.) and N-tert-butoxycarbonyl-L-serine (obtained from U.S. Biochemical Corporation) were dried over P₂O₅ for 72 hr and 24 hr, respectively. Tetrahydrofuran was distilled from sodium benzophenone ketyl directly into the glassware (under argon) the day before and stored under argon overnight until used.

3. The temperature of the solution should be about -75°C before the diethyl azodicarboxylate is added.

4. Diethyl azodicarboxylate was obtained from Fluka AG. The material used was distilled, bp 82-83°C at 2 mm, in the hood behind a safety shield. It is important that the addition of this compound to the reaction mixture be done at a constant rate without interruption because of its tendency to freeze in the syringe needle. Dimethyl azodicarboxylate (17.7 mL, 160 mmol; d = 1.33 g/mL at 25°C; bp 71-72°C at 2 mm) can be used in place of diethyl azodicarboxylate. This compound is manufactured by Tokyo Kasei Kogyo Co. and is available from CTC Organics.

5. The solution of dried N-(tert-butoxycarbonyl)-L-serine was made up separately in an addition funnel under an atmosphere of argon. This avoids complications that may arise if the funnel is prefitted on the reaction vessel.

6. The reaction vessel was placed in a water bath at room temperature after the temperature of the mixture was ca. 15°C.

7. The reaction usually works better on a smaller scale (25 mmol) where a yield of 70% or greater can be obtained. The flash column was eluted such that the solvent level dropped 1 cm/13 sec. This corresponds to an approximate rate of 362 mL/min. The concentration and purification of the reaction mixture should be done as quickly as possible on the same day. Although storage of the concentrated reaction mixture at -20°C overnight results in substantial decomposition of the lactone, column fractions containing pure lactone (after chromatography) can be stored at 4°C overnight and concentrated on the following day.

The β -lactone is readily visualized by TLC (Merck, Kieselgel 60 F₂₅₄, 0.25 mm thickness, hexane/ethyl acetate (65/35) as solvent system) by staining in iodine or by using bromocresol green spray (0.04% in EtOH, made blue by NaOH) followed by heating the plate to detect the lactone as a yellow spot on a blue background.

8. The product exhibits the following properties: mp 119.5-120.5°C; $[\alpha]_D^{24}$ -26.2° (CH₃CN, c 1); IR cm⁻¹: 3358, 1836, 1678, 1533, 1290, 1104; ¹H NMR (360 MHz, CD₂Cl₂) δ : 1.45 (s, 9 H, -C(CH₃)₃), 4.4-4.45 (m, 2 H, CH₂), 4.95-5.05 (m, 1 H, NH-CH), 5.2-5.4 (br s, 1 H, NH); MS (CI, NH₃), m/z 205 (M-NH₄⁺, 100%). Anal. Calcd for C₈H₁₃NO₄: C, 51.33; H, 6.99; N, 7.48. Found: C, 51.28; H, 7.01; N, 7.42.

9. Anhydrous p-toluenesulfonic acid was prepared from the monohydrate (obtained from Aldrich Chemical Company, Inc.) by solution in hot benzene with the aid of ethyl acetate and azeotropic distillation to 50% volume to remove water. The solution was then concentrated to a syrup on a rotary evaporator. The syrup was dissolved in a minimum volume of acetone and excess benzene was added to

precipitate the anhydrous acid. This material was recrystallized from acetone/benzene and dried at 50°C for 12 hr. It was stored under reduced pressure over anhydrous CaSO_4 . The material used melted at 104-105°C.

10. Trifluoroacetic acid (obtained from Aldrich Chemical Company, Inc.) was refluxed over P_2O_5 for ca. 3 hr and then distilled from P_2O_5 under an atmosphere of argon. The material used distilled at 68-71°C. All manipulations involving trifluoroacetic acid (except removal on a rotary evaporator) were done in a fume hood.

11. Commercially available anhydrous ether (obtained from Fisher Scientific Company) was used directly from a freshly opened can.

12. The product exhibits the following properties: mp ($\sim 4^\circ\text{C}/\text{min}$) 133-135°C (darkens), 173°C (dec) (rapid); $[\alpha]_{\text{D}}^{24} -15.8^\circ$ (DMF, c 2.2); IR (Fluorolube mull) cm^{-1} : 3040, 1833, 1547; ^1H NMR (360 MHz, d_7 DMF) δ : 2.3 (s, 3 H, ArCH_3), 4.66 (m, 1 H, CHHO), 4.74 (m, 1 H, CHHO), 5.54 (dd, 1 H, $J = 4.6, 6.5$, CH), 7.15 (d, 2 H, $J = 8$, m-ArH), 7.64-7.7 (d, 2 H, $J = 8$, o-ArH); FAB MS (glycerol) m/z 260 (MH^+). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_5\text{S}$: C, 46.32; H, 5.05; N, 5.40; S, 12.37. Found: C, 46.44; H, 5.14; N, 5.24; S, 12.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

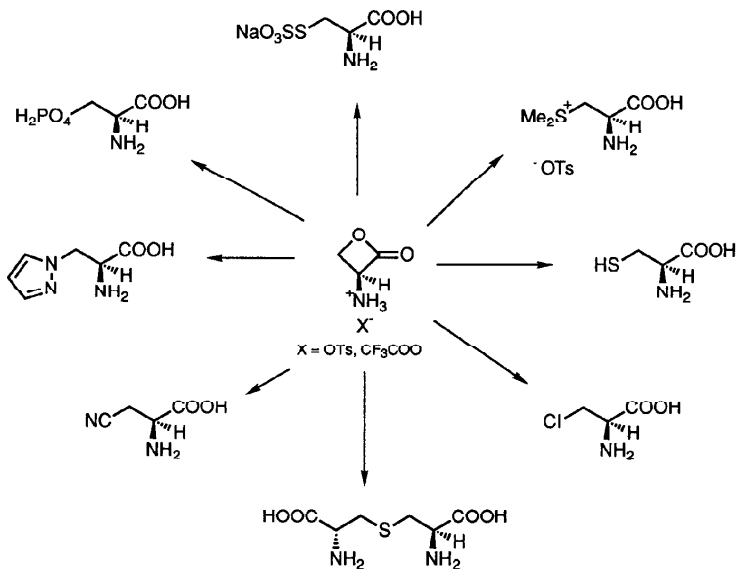
3. Discussion

Recent work has shown that a large variety of carbon, nitrogen, oxygen, sulfur, and halogen nucleophiles attack chiral N-protected serine β -lactones at the β -carbon to give optically pure N-protected α -amino acids.^{2,4} However in certain cases (e.g., β -azidoalanine⁵) these products are unstable to most common deprotection conditions. The procedure given here describes the preparation of (S)-3-amino-2-oxetanone p-toluenesulfonic acid salt, a compound which reacts with a variety of nucleophiles to afford unprotected, optically pure α -amino acids directly (Scheme 1).⁶ This salt has a long shelf life (many months) at room temperature provided that it is stored dry. It reacts rapidly with water ($t_{1/2} \sim 2.5$ hr in unbuffered water; $t_{1/2} \sim 10$ min in 50 mM potassium phosphate at pH 6.8). However, good nucleophiles such as thiols afford high yields of sulfur-containing amino acids in water if the pH is kept at 5.0-5.5.⁶ Since both enantiomers of serine are relatively inexpensive, and L-serine is readily available in isotopically labeled form, this approach should prove useful for syntheses of sensitive D-amino acids as well as for preparation of the labeled L-isomers.

1. Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2.
2. (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105; (b) Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649.
3. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
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Scheme 1



Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-tert-Butoxycarbonyl-L-serine β -lactone: Carbamic acid, (2-oxo-3-oxetanyl)-, 1,1-dimethylethyl ester, (S)- (11); (98541-64-1)

(S)-3-Amino-2-oxetanone p-toluenesulfoante: 2-Oxetanone, 3-amino-, (S)-, 4-methylbenzenesulfonate (12); (112839-95-9)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

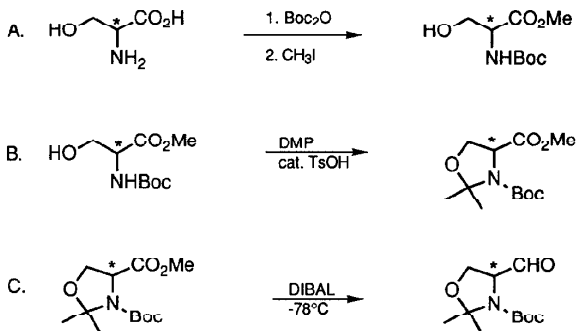
Diethyl azodicarboxylate: Formic acid, azodi-, diethyl ester (8); Diazenedicarboxylic acid, diethyl ester (9); (1972-28-7)

N-tert-Butoxycarbonyl-L-serine: Serine, N-carboxy-, N-tert-butyl ester, L- (8); L-Serine, N[(1,1-dimethylethoxy)carbonyl]- (9); (3262-72-4)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

**1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-
3-OXAZOLIDINECARBOXYLATE: A USEFUL SERINAL DERIVATIVE**
(3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-,
1,1-dimethyl ester, (S)- or (R)-)



Submitted by Philip Garner and Jung Min Park.¹

Checked by Mayumi Takasu and Hisashi Yamamoto.

1. Procedure

A. *N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester*. A solution of di-tert-butyl dicarbonate [(Boc)₂O] (78.4 g, 0.36 mol, Note 1) in dioxane (280 mL, Note 2) is added to an ice-cold, magnetically stirred solution of L-serine (31.7 g, 0.30 mol, Note 3) in 1 N sodium hydroxide (620 mL) by means of an addition funnel. The two-phase mixture is stirred at 5°C for 30 min, then allowed to warm to room temperature over 3.5 hr at which time TLC analysis shows the reaction to be complete (Note 4). The mixture is concentrated to half its original volume by rotary evaporation at 35°C, cooled in an

ice-water bath, acidified to pH 2-3 by the slow addition of 1 N potassium bisulfate (620 mL), and then extracted with ethyl acetate (3 x 1000 mL). The combined extracts are dried over magnesium sulfate, filtered and concentrated to give N-Boc-L-serine (63.0 g) as a colorless, sticky foam which is used without further purification.

To a cold solution of N-Boc-L-serine (32.4 g, 0.16 mol, Note 5) in dimethylformamide (150 mL) is added solid potassium carbonate (24.3 g, 0.176 mol). After stirring for 10 min in an ice-water bath, methyl iodide (20.0 mL, 46.3 g, 0.32 mol - *Caution! Methyl iodide is toxic and a suspected carcinogen that should be handled in a well-ventilated fume hood.*) is added to the white suspension and stirring continued at 0°C for 30 min whereupon the mixture solidifies. The reaction is warmed to room temperature and stirred for an additional hour or so at which point TLC analysis indicates complete formation of the methyl ester (Note 6). The reaction mixture is filtered by suction and the filtrate partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase is washed with brine (2 x 300 mL), dried with magnesium sulfate, filtered and concentrated to give 29.8 g (86% yield) of N-Boc-L-serine methyl ester as a pale amber oil which is used without further purification (Notes 7 and 8).²

B. 3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate. To a 2-L. three-necked, round-bottomed flask, equipped with a magnetic stirring bar, Claisen distilling head, thermometer, and reflux condenser protected from moisture by a calcium sulfate-filled drying tube are added a solution of N-Boc-L-serine methyl ester (48.5 g, 0.22 mol) in benzene (770 mL), 2,2-dimethoxypropane (55 mL, 47 g, 0.45 mol), and p-toluenesulfonic acid monohydrate (0.593 g, 3.1 mmol, Note 9). The colorless solution is heated under reflux (oil bath temperature, 110°C) for 30 min, then slowly distilled until a volume of 660 mL is collected over 4 hr when the reaction is judged to be complete by TLC (Notes 10 and 11). The cooled, amber solution is partitioned between saturated sodium bicarbonate solution (200 mL) and ethyl ether

(2 x 500 mL). The organic layer is washed with brine (200 mL), then dried over magnesium sulfate, filtered and concentrated to give the crude product as an amber oil. This material is vacuum distilled through a 10-cm Vigreux column to give 40.3-50.9 g (70-89% yield) of oxazolidine methyl ester as a very pale yellow liquid, bp 101-102°C (2 mm) (Note 12).

C. *1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate*. A dry (Note 13), 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septa, three-way balloon adapter, and a low temperature thermometer. After the flask is purged with nitrogen (Note 14), a solution of the oxazolidine ester (40.2 g, 0.15 mol) in dry toluene (300 mL, Note 15) is added via cannula (using positive nitrogen pressure) and cooled to -78°C with an acetone-dry ice bath. To this cooled solution is added a -78°C solution of 1.5 M diisobutylaluminum hydride in toluene (175 mL, Note 16) via cannula (using positive nitrogen pressure). The rate of addition is adjusted so as to keep the internal temperature below -65°C and takes approximately 1 hr to complete. The reaction mixture is stirred for an additional 2 hr at -78°C under an atmosphere of nitrogen when TLC analysis shows the reaction to be complete (Note 17). The reaction is quenched by slowly adding 60 mL of cold (-78°C) methanol (*Evolution of hydrogen occurs!*) - again so as to keep the internal temperature below -65°C. The resulting white emulsion is slowly poured into 1000 mL of ice-cold 1 N hydrochloric acid with swirling over 15 min, and the aqueous mixture is then extracted with ethyl acetate (3 x 1000 mL). The combined organic layers are washed with brine (1000 mL), dried over magnesium sulfate, filtered and concentrated to give 33.6 g of crude product as a colorless oil. This material is vacuum distilled through a 10-cm Vigreux column to give 26.9 g (76% yield) of oxazolidine aldehyde as a colorless liquid, bp 83-88°C (1.0-1.4 mm) (Note 18).

2. Notes

1. The submitters used di-tert-butyl dicarbonate purchased from Aldrich Chemical Company, Inc., also available from Wako Pure Chemical Industries, LTD.

2. Unless stated otherwise in the procedure, all solvents and reagents were used as purchased without further purification.

3. The submitters used L-serine (and D-serine) purchased from United States Biochemical Corporation, also available from Tokyo Kasei Kogyo Co., LTD.

4. TLC analysis on Merck silica gel 60F-254 plates eluting with (8:1:1) n BuOH-H₂O-AcOH showed the clean formation of a product with R_f 0.65 (visualized with 0.3% ninhydrin in (97:3) n-BuOH-AcOH) at the expense of starting amino acid at the origin. If starting material remained, more (Boc)₂O (13.1 g, 0.060 mol) was added.

5. The submitters have also found commercially available N-Boc-L-serine (United States Biochemical Corporation) to be an entirely satisfactory starting material. However, for the unnatural D-series, they find that it is more economical to prepare N-Boc-D-serine as described.

6. TLC analysis on Merck silica gel 60F-254 plates eluting with (1:1) ethyl acetate-hexanes showed the clean formation of ester, R_f 0.38 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), at the expense of starting material at the origin.

7. Optical measurements on this material were not very useful since they were in general low and quite variable. Furthermore, no literature values could be found for comparison. IR (neat) cm⁻¹: 3400, 1720 (br); ¹H NMR (200 MHz, C₆D₆, 17°C) δ: 1.41 (s, 9 H), 2.50 (br, s, H, exchanged with D₂O), 3.26 (s, 3 H), 3.66 (dd, H, J = 11 and 4), 3.76 (dd, H, J = 11 and 4), 4.40 (m, H), 5.60 (m, H, exchanged with D₂O).

8. *Alternatively, the methyl ester could be prepared as follows:* N-Boc-serine (63 g, 0.31 mol) was dissolved in ethyl ether (600 mL) in a 2-L Erlenmeyer flask equipped with a magnetic stirring bar, cooled in an ice-water bath and treated with ten 50-mL aliquots of cold ethereal (approximately 0.6 M) diazomethane prepared from N-nitroso-N-methylurea according to Arndt's procedure.³ After 30 min at 0°C, TLC analysis showed the reaction to be complete (Note 6). Excess diazomethane was destroyed with acetic acid (the yellow color disappears) and the resulting solution was extracted with half-saturated sodium bicarbonate solution (300 mL), then washed with brine (200 mL), dried with magnesium sulfate, filtered and concentrated to give 60.1 g (91% over 2 steps) of N-Boc-serine methyl ester as a colorless, sticky foam which was used without further purification. *Caution! N-Nitroso-N-methylurea is suspected of being a carcinogen and diazomethane is highly toxic. The utmost care must be used when handling these substances: diazomethane solutions should be restricted to a well-ventilated fume hood at all times.*

9. Moriwake et al. have reported that boron trifluoride etherate can also be used as the acid catalyst for this reaction.⁶

10. TLC analysis on Merck silica gel 60F-254 plates eluting with (1:1) ethyl acetate-hexanes showed the clean formation of product, R_f 0.78 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), at the expense of starting material at R_f 0.23.

11. If starting material remained at this time, more 2,2-dimethoxypropane (14 mL, 12 g, 0.11 mol) and benzene (310 mL) were added and the procedure was repeated, collecting 250 mL of distillate, at which time the TLC analysis generally showed the reaction to be complete.

12. The optical rotation of the L-oxazolidine methyl ester was -46.7° (CHCl_3 , c 1.30). An essentially identical procedure emanating from N-Boc-D-serine methyl ester gave the corresponding D-oxazolidine methyl ester in 80% yield with a rotation of $+53^\circ$. In either case further purification could be achieved with flash chromatography

to give product with a maximum rotation of 57° although we have found distilled material to be entirely satisfactory for our purposes: IR (neat) cm^{-1} : 1760, 1704; ^1H NMR (200 MHz, C_6D_6 , 75°C) δ : 1.41 (s, 9 H), 1.53 (br s, 3 H), 1.81 (br s, 3 H), 3.35 (s, 3 H), 3.75 (dd, H, $J = 8.5$ and 8.1), 3.81 (dd, H, $J = 8.5$ and 3.5), 4.26 (m, H). (The oxazolidine derivatives exist as slowly interconverting rotamers on the NMR time scale and samples require heating to obtain averaged spectra.)

13. All the glassware (except the low-temperature thermometer) was oven-dried ($>100^\circ\text{C}$) and quickly assembled before use.

14. The checkers used argon.

15. Toluene was distilled from sodium-benzophenone ketyl.

16. The diisobutylaluminum hydride solution (1.5 M in toluene, Aldrich Chemical Company, Inc.) was transferred to a dry, 250-mL, graduated cylinder equipped with a rubber septum and drying tube via cannula (using positive nitrogen pressure). The graduated cylinder was then placed in a Dewar flask and cooled to -78°C with an acetone-dry ice bath.

17. TLC analysis on Merck silica gel 60F-254 plates eluting with (4:1) hexanes-ethyl acetate showed the formation of product, R_f 0.33 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), with only a trace of starting material remaining at R_f 0.41. Some over-reduced product arising within the TLC capillary may be evident at this stage.

18. The optical rotation of the L-oxazolidine aldehyde was -91.7° (CHCl_3 , c 1.34). An identical procedure emanating from the D-oxazolidine methyl ester gave D-oxazolidine aldehyde in 85% yield having a rotation of $+95^\circ$. These distilled products contained up to 5% of the starting material as judged by their NMR spectra, but were suitable for use without further purification. Homogeneous samples could be obtained in either case by flash chromatography on silica gel eluting with (4:1) hexanes-ethyl acetate and showed a maximum optical rotation of 105° . This material can be stored

indefinitely provided it is kept cold ($\leq 5^{\circ}\text{C}$) and moisture-free. IR (neat) cm^{-1} : 1735, 1705; ^1H NMR (200 MHz, C_6D_6 , 60°C) δ : 1.34 (s, 9 H), 1.40 (br s, 3 H), 1.59 (br s, 3 H), 3.52 (dd, H, $J = 8.7$ and 8.3), 3.65 (dd, H, $J = 8.7$ and 2.9), 3.90 (m, H), 9.34 (br s, H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

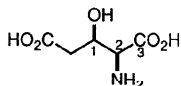
Since its preparation and use was first reported by us,⁴ the title compound has been gaining favor as a chiral, nonracemic synthon for the asymmetric synthesis of a variety of amino alcohol- and amino acid-containing targets. Among the virtues of this oxazolidine aldehyde over previously reported N-acylated serinal derivatives are its ease of preparation on a large scale and its configurational stability. The procedure described here provides material that has been determined to be 95% enantiomerically pure by Mosher ester analysis.⁷ Homologation (C-C bond formation) of this serinal derivative can be achieved without competing racemization using both olefination^{6,15,22-26} and nucleophilic addition^{4,5,8-14,16-21} protocols. The latter process can be made to occur with good to excellent diastereoselectivity (i.e., 1,2-asymmetric induction) by simply choosing reagents/conditions so as either to preclude or favor chelation-control. Protocols for diastereoselective additions to the oxazolidine appended olefins are also known. Once the rest of the target molecule's structure is in place, the oxazolidine can be unravelled to give either an aminoethanol group or, after oxidation of the primary alcohol, an α -amino acid moiety. The products so produced

are typically >98% enantiomerically pure. Thus the title compound can serve not only as a serinal derivative but as a penaldic acid equivalent as well. Representative examples of the use of 1,1-dimethylethyl (S)- and (R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate as a chiral synthon for natural product synthesis are collected in Table I.

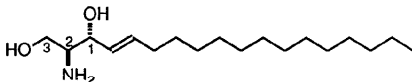
1. Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106-7078.
2. We thank Dr. N. S. Chandrakumar of G. D. Searle and Company for alerting us to the fact that N-Boc-serine methyl ester could be prepared without significant racemization via esterification with methyl iodide, thereby avoiding the generation and use of diazomethane on a large scale.
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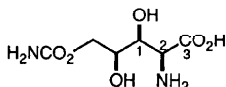
TABLE
 SELECTED EXAMPLES OF THE USE OF 1,1-DIMETHYL (S)- AND (R)-4-FORMYL-
 2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE FOR NATURAL PRODUCT
 SYNTHESIS: THE C-3 SUBUNITS EMANATING FROM SERINE
 ARE NUMBERED ACCORDINGLY



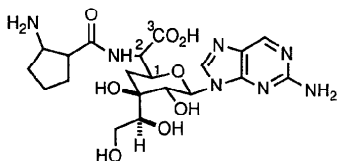
threo-β-hydroxy-L-glutamic acid (ref. 4)



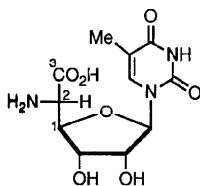
D-erythro-sphingosine (refs. 8-10,12,13)



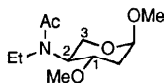
5-carbamoylpolyoxamic acid (ref. 11)



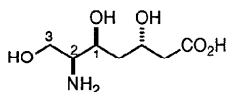
Amipurimycin studies (ref. 5)



Thymine polyoxin C (ref. 16)



Calicheamycin fragment (ref. 19)



(-)-Galantic acid (ref. 26)

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,1-Dimethylethyl (S)- or (R)-4-formyl-2,2-dimethyloxazolidinecarboxylate:

3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)- or (R)- (11); (S)- (102308-32-7); (R)- (95715-87-0)

N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester: L-Serine,

N-[(1,1-dimethylethoxy)carbonyl]-, methyl ester (9); (2766-43-0)

Di-tert-butyl dicarbonate: Formic acid, oxydi-, di-tert-butyl ester (8);

Dicarboxylic acid, bis(1,1-dimethylethyl) ester (9); (24424-99-5)

Serine: L-Serine (8,9); (56-45-1)

N-tert-Butoxycarbonylserine: Serine, N-carboxy-, N-tert-butyl ester, L- (8);

L-Serine, N-[(1,1-dimethylethoxy)carbonyl]- (9); (3262-72-4)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate:

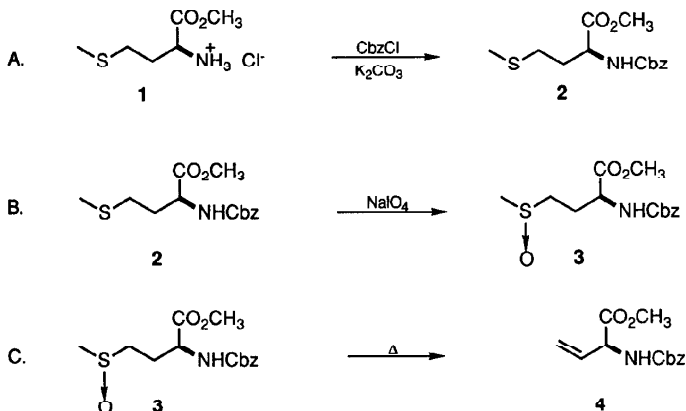
3,4-Oxazolidinedicarboxylic acid, 2,2-dimethyl-, 3-(1,1-dimethylethyl) 4-methyl ester, (S)- (12); (108149-60-6)

p-Toluenesulfonic acid monohydrate (8) Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

Diisobutylaluminum hydride: Aluminum, hydrodiisobutyl- (8); Aluminum, hydrobis(2-methylpropyl)- (9); (1191-15-7)

Nitrosomethylurea: Urea, N-methyl-N-nitroso-; (684-93-5)

N-(BENZYLOXYCARBONYL)-L-VINYLGLYCINE METHYL ESTER
(3-Butenoic acid, 2-[[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)-)



Submitted by Michael Carrasco, Robert J. Jones, Scott Kamel, H. Rapoport,¹
 and Thien Truong.

Checked by Antje Grützmann and Ekkehard Winterfeldt.

1. Procedure

A. *N*-(Benzyloxycarbonyl)-L-methionine methyl ester (2). A 3-L, three-necked, Morton flask equipped with an efficient mechanical stirrer, thermometer, and a dropping funnel is charged with L-methionine methyl ester hydrochloride (117.6 g, 0.56 mol) (Note 1), potassium bicarbonate (282.3 g, 2.82 mol, 500 mol %), water (750 mL), and ether (750 mL), and the solution is cooled to 0°C. Benzyl chloroformate (105

g, 88.6 mL, 0.62 mol, 110 mol %, Aldrich Chemical Company, Inc.) is added dropwise over 1 hr, the cooling bath is removed, and the solution is stirred for 5 hr. Glycine (8.5 g, 0.11 mol, 20 mol %, Aldrich Chemical Company, Inc.) is added (to scavenge excess chloroformate) and the solution is stirred for an additional 18 hr. The organic layer is separated, and the aqueous layer is extracted with ether (2 x 200 mL). The combined organic layers are washed with 0.01 M hydrochloric acid (2 x 500 mL), water (2 x 500 mL), and saturated brine (500 mL), and then dried (Na_2SO_4), filtered, and evaporated on a rotary evaporator. The resulting oil is further dried in a Kugelrohr oven (50°C, 0.1 mm, 12 hr) to leave product **2** as a clear oil that solidifies upon cooling: 165-166 g (98-99%), mp 42-43°C.

B. Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate (3). A 5-L, three-necked, Morton flask equipped with an efficient mechanical stirrer, thermometer, and dropping funnel is charged with **2** (166.0 g, 0.56 mol) and methanol (1.5 L), and the solution is cooled to 0°C. A solution of sodium periodate (NaIO_4) (131.4 g, 0.61 mol, 110 mol %) in water (2 L) is added dropwise over a period of 1.5 hr. The cooling bath is removed and the mixture is stirred for 18 hr. The product is vacuum-filtered through Celite and divided into two portions. Each portion is extracted with chloroform (6 x 200 mL), washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4), filtered, and evaporated by rotary evaporation (bath temperature <30°C). The resulting oils are combined and further dried in a Kugelrohr oven (30°C, 0.1 mm, 12 hr), yielding the product as a waxy solid: 173.2 g, 99%.

C. N-(Benzyloxycarbonyl)-L-vinylglycine methyl ester (4). Sulfoxide **3** (35.0 g, 0.11 mol) and Pyrex helices (35 g) are placed in a 1-L, round-bottomed flask, thoroughly mixed by shaking, and distilled from a rocking Kugelrohr apparatus (195-200°C, 0.1-0.3 mm, 1 hr) into a chilled receiving flask cooled in powdered dry ice to afford a yellow oil (Notes 2 and 3). Low pressure chromatography (LPC) of the crude oil gives the N-protected vinylglycine methyl ester **4** (17.4 g, 62%) of 95% purity (Notes

4 and 5). Medium pressure liquid chromatography (MPLC) of the crude oil provides pure 4 in 60% yield from 3 (Note 6). L-Vinylglycine hydrochloride can be obtained from 4 in almost quantitative yield by refluxing in 6 N hydrochloric acid for 1 hr.²

2. Notes

1. L-Methionine methyl ester hydrochloride is commercially available (Aldrich Chemical Company, Inc.); however, it is prepared easily as follows: A 3-L, three-necked, Morton flask is equipped with an efficient mechanical stirrer. The flask is charged with L-methionine (100.0 g, 0.67 mol) and methanol (0.7 L), the solution is cooled to 0°C, and hydrogen chloride gas is bubbled through the mixture for 15 min (in about 2 min the solution becomes homogeneous). The cooling bath is removed, the solution is stirred for 18 hr, and the solvent is evaporated. Further drying under reduced pressure gives L-methionine methyl ester hydrochloride as a white solid (132.5 g, 99%), that is suitable for most purposes. It can be recrystallized by dissolving in hot methanol (500 mL) and precipitating with ether (1 L) to give the pure hydrochloride: 117.6 g, 88%, mp 152-153°C.

2. *Caution: Stench. The entire reaction apparatus -- Kugelrohr oven, vacuum pump, and subsequent chromatography -- should be kept in an efficient fume hood.*

3. TLC of the distillate shows 4 (2/1, hexanes/ethyl acetate; visualization by staining with 5% ethanolic molybdophosphoric acid and charring) as the major product (R_f 0.37) along with minor amounts of the (E)- and (Z)- α,β -unsaturated isomer (R_f 0.40 and 0.30).

4. LFC conditions are as follows: 9-cm diameter column; 800 mL of 230-400 mesh EM Science silica gel; 4/1, hexanes/ethyl acetate (1.8 L) to 2/1, hexanes/ethyl acetate.

5. The ^1H NMR spectrum of **4** is as follows: (CDCl_3) δ : 3.77 (s, 3 H, CO_2CH_3), 4.94 (m, 1 H, $\alpha\text{-H}$), 5.13 (s, 2 H, CH_2PH), 5.28 (dd, 1 H, $J = 1.2, 10.3$, H_{cis}), 5.36 (dd, 1 H, $J = 1.4, 17.1$, H_{trans}), 5.47 (bd, 1 H, NH), 5.91 (m, 1 H, H_{vinyl}), 7.35 (s, 5 H, ArH).

6. MPLC conditions are as follows: 40 cm x 6-cm column; 230-400 mesh EM Science silica gel; flow rate 18 mL/min; model 153 Altex UV Detector; retention time ca. 100 min; 4/1, hexanes/ethyl acetate. The distillate was chromatographed in 2.5-g batches. The checkers experienced significant losses in this step, which may be highly sensitive to the type of silica and the apparatus used. In any case the material obtained after the first chromatography will be acceptable for most purposes.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories", National Academy Press; Washington, DC, 1983.

3. Discussion

Vinylglycine is a natural amino acid found in mushrooms.³ It is an inhibitor of pyridoxal-linked aspartate aminotransferase,⁴ and has also been postulated as an intermediate in the enzymatic conversion of homoserine to threonine⁵ and α -ketobutyrate.⁶ Protected vinylglycine is also a versatile asymmetric starting material for synthesis.⁷ Variants have been prepared in racemic,⁸⁻¹³ optically active,¹⁴ optically pure,^{2,15-17} and isotopically labeled form.^{4b,18-20} This procedure is derived from our earlier publication² and contains improvements in procedure and scale-up.

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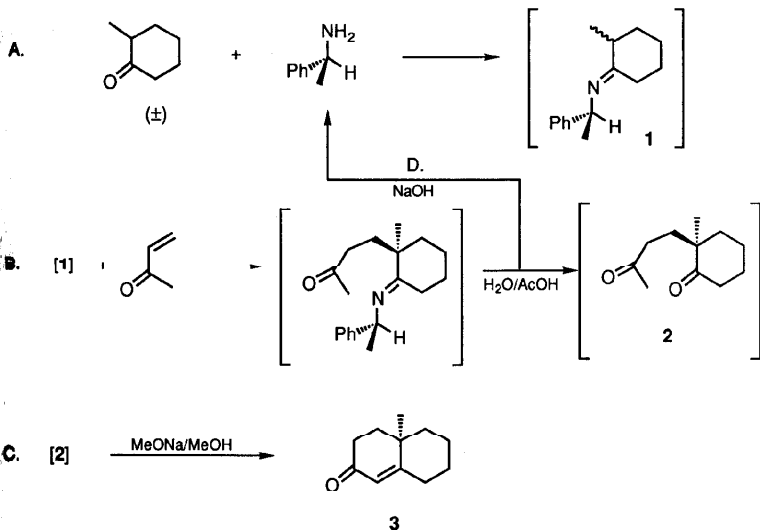
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- N-(Benzyloxycarbonyl)-L-vinylglycine methyl ester: 3-Butenoic acid, 2-[[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)- (10); (75266-40-8)
- N-(Benzyloxycarbonyl)-L-methionine methyl ester: L-Methionine, N-[(phenylmethoxy)carbonyl]-, methyl ester (9); (56762-93-7)
- L-Methionine methyl ester hydrochloride: Methionine, methyl ester, hydrochloride, L- (8); L-Methionine, methyl ester, hydrochloride (9); (2491-18-1)
- Benzyl chloroformate: Formic acid, chloro-, benzyl ester (8); Carbonochloride acid, phenylmethyl ester (9); (501-53-1)
- Glycine (8,9); (56-40-6)
- Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate: Butanoic acid, 4-(methylsulfinyl)-2-[[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)- (10); (75266-39-3)
- L-Vinylglycine hydrochloride: 3-Butenoic acid, 2-amino-, hydrochloride, (S)- (10); (75266-38-5)
- L-Methionine (8,9); (63-68-3)

(R)-(-)-10-METHYL-1(9)-OCTAL-2-ONE

(2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4a-methyl-, (R)-)



Submitted by G. Revial and M. Pfau.¹

Checked by Graham N. Maw and Robert K. Boeckman, Jr.

1. Procedure

A. Imines (1). In a 1000-mL, round-bottomed flask, fitted with a toluene-filled Dean-Stark water separator, 100.0 g (0.825 mol) of (S)-(-)- α -methylbenzylamine (Note 1), 92.5 g (0.825 mol) of 2-methylcyclohexanone (Note 2) and 100 mL of toluene

are heated at reflux temperature under a nitrogen atmosphere. After 24 hr, ca. 15 mL of water (ca. 100% theor.) has been removed azeotropically.

B. (R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone (2). The solution of imines **1** is cooled in an ice bath and 72.5 mL (61.0 g, 0.870 mol, ca. 1.05 equiv) of freshly distilled methyl vinyl ketone (Note 3) is added with a syringe, with magnetic stirring, under a nitrogen atmosphere. The flask is then heated at ca. 40°C for 24 hr.

The slightly yellow solution is cooled in an ice bath and 60 mL of glacial acetic acid (ca. 1 mol) and 50 mL of water are added. Hydrolysis is achieved by stirring the heterogeneous mixture at room temperature for 2 hr. The now clear solution is poured into a 2000-mL separatory funnel containing 100 mL of brine and 160 mL of water and is extracted five times with a 50:50 mixture of ether-petroleum ether (35-60°C) (1000-mL total amount). The organic phase is washed efficiently with 20 mL of 10% hydrochloric acid, 20 mL of water, and two 10-mL portions of brine.

The aqueous layer is kept for recovery of the amine (see D below).

The pale yellow organic layer is dried over a small amount of anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator at ca. 40°C and the crude diketone **2** (ca. 145 g) is used directly for the next step.

C. (R)-(-)-10-Methyl-1(9)-octal-2-one (3). Dry methanol (600 mL) is added to the crude diketone **2** contained in a 2000-mL, round-bottomed flask and a rubber septum is fitted. The solution is stirred at room temperature for 15 min under a slight stream of nitrogen to remove traces of oxygen. A 25 wt. % solution of sodium methoxide in methanol (Note 4) is then introduced dropwise with a syringe, under stirring, until a slightly red color develops (Note 5). At this point, 15 mL (ca. 0.07 mol) of the sodium methoxide solution is added and the mixture is heated at 60°C for 10 hr under a nitrogen atmosphere. The solution is cooled and the now deep red solution is neutralized with glacial acetic acid (ca. 4.5 mL) until the color turns yellow. Methanol is removed with a rotary evaporator until a thick paste (sodium acetate) results; this is

dissolved with 200 mL of water. Extraction is effected in a 2000-mL separatory funnel using four portions of a 50:50 mixture (1000 mL total amount) of ether-petroleum ether (35-60°C). The pale orange organic phase is washed twice with 40 mL of water, then twice with 20 mL of brine. The organic layer is dried over a small amount of anhydrous magnesium sulfate and filtered. The solvents are removed with a rotary evaporator at ca. 40°C and the red oily residue of crude octalone **3** is distilled under reduced pressure to afford ca. 110 g of a colorless oil, bp 70°C (2 mm) (Note 6). The oil is purified by recrystallization at a low temperature with an apparatus designed for this purpose.² The oil is dissolved with stirring in a 1000-mL, round-bottomed flask with 370 mL of pentane under a nitrogen atmosphere. The flask is then cautiously cooled in a Dewar flask containing liquid nitrogen until the solution is solid. The Dewar flask is removed and the temperature is allowed to rise, while magnetic stirring is resumed. When a crystalline mass in suspension appears suddenly (Note 7), an acetone bath adjusted to about -10°C is installed. When only a few crystals remain in suspension, the bath temperature is slowly lowered to -35°C, inducing crystallization. After the mixture has been kept at -35°C for 15 min, magnetic stirring is stopped and efficient filtration is performed through the filter stick. Still at -35°C, the compound is washed with 40 mL of pentane. The solution is stirred vigorously for 5 min and filtered as before. The washing operation is repeated two more times. The flask is warmed to room temperature and the oil is distilled as before, bp 70°C (2 mm), to afford 60-65 g (44-48% overall yield from 2-methylcyclohexanone) of methyloctalone **3** [>99% chemical purity, capillary GLC (Note 6)], $[\alpha]_{\text{D}}^{20}$ -210° (ethanol, c 1.00), optical purity 96% (Note 8).

D. Recovery of (S)-(-)- α -methylbenzylamine. The aqueous layer (see above, **B**, 3rd paragraph) contained in a 1000-mL flask is cooled in an ice bath under a nitrogen atmosphere. An aqueous 10% sodium hydroxide solution is added with stirring until a pH of 12-14 (Note 9) is reached. The mixture is transferred to a

2000-mL separatory funnel and extracted three times with ether (1000-mL total amount). The organic phase is washed twice with 100 mL of water and twice with 30 mL of brine, then dried over potassium carbonate and filtered. The solution is concentrated at room temperature with a rotary evaporator and distilled under reduced pressure to afford 85-90 g (85-90% yield) of the amine, bp 70°C (15 mm), the specific rotation of which is the same as that of the original starting material.

2. Notes

1. (S)-(-)- α -Methylbenzylamine (95.8% optical purity) and its (R)-(+)-enantiomer (93.4% optical purity) were purchased from Aldrich Chemical Company, Inc. and used without further purification. *Caution: These amines are toxic.* Air must be excluded to prevent formation of carbonates.

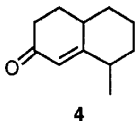
2. 2-Methylcyclohexanone was purchased from Aldrich Chemical Company, Inc., and used without further purification.

3. Methyl vinyl ketone, purchased from Aldrich Chemical Company, Inc., is dried over anhydrous potassium carbonate for 0.5 hr. The now slightly-colored oil is filtered and distilled under a nitrogen atmosphere at reduced pressure, bp 55°C (260 mm). *The colorless center of the distillate is collected over a few milligrams (ca. 0.05% concentration) of hydroquinone.*

4. A 25 wt % solution of sodium methoxide in methanol (4.6 M) was purchased from Aldrich Chemical Company, Inc.

5. Any acetic acid present is thus neutralized (a few drops are usually sufficient). Confirm that a basic pH has been reached by testing a drop of the solution, removed by syringe.

6. Although a TLC test (silica gel Merck 60 F₂₅₄, ethyl acetate/hexane 20:80 elution, UV and chromic-sulfuric acid visualization) of this oil reveals only one spot (R_f 0.6), capillary GLC (Hewlett-Packard HP-5, 25 m x 0.2 mm x 0.5 μ m, 200°C) shows in addition to methylcyclohexanone **3** (retention time, 10.9 min), an 8% impurity (retention time, 11.7 min) which is probably the regioisomer **4**.



A chemically pure sample of methylcyclohexanone **3**, $[\alpha]_D^{20}$ -190° (ethanol, c 1.00) is obtained by preparative GLC (3 m x 1/4", 5% carbowax 20 M on Aeropak 30, 180°C, retention time 12.4 min) of a distillate sample. The impurity has a 13.2-min retention time under these conditions. A good approximation of the reaction ee is calculated as follows, taking into account the optical purity of the starting amine (95.8%) and the $[\alpha]_D^{20}$ -219° (ethanol, c 1.00) value (Note 8) for optically pure methylcyclohexanone **3**: $ee = 100 \times 190 \times 100/95.8 \times 219 \cong 91\%$.

7. If no crystalline mass is formed but instead an emulsion of the two liquid phases appears, the entire solidification must be repeated (liquid nitrogen cooling).

8. Optically pure methylcyclohexanone **3** is obtained by recrystallizing a sample of the purified compound several times until a constant $[\alpha]_D^{20}$ -219° (ethanol, c 1.00 or methanol, c 1.10) is observed. The $[\alpha]_D^{20}$ -219° (methanol, c 1.1) value from the literature³ is confirmed.

9. If a pH lower than 12 is used, recovery of the amine is poor.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

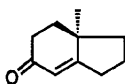
Optically active methyloctalone **3** (or its enantiomer) has been obtained by resolution^{3,4} and by asymmetric synthesis.⁵ Both enantiomers are also available commercially. The synthesis described here is by far the most simple and gives the best yield. It is an application of the general method reported for the enantioselective elaboration of quaternary carbon centers through Michael-type alkylation of chiral imines.⁶

This general method has the following advantages: very simple procedures, very mild conditions involving moderate reaction temperatures and no acids, bases, catalysts, etc., allowing the use of labile reactants, excellent regio- and enantioselectivities as well as high chemical yields, and creation of useful chiral building blocks with quaternary carbon centers involving functionalized chains, allowing one to devise syntheses of natural compounds of various types (terpenes, steroids, alkaloids, etc.). As both optically active amines are commercially available, targets with either desired absolute configuration can be synthesized. Easy recovery of the auxiliary chiral moiety is possible.

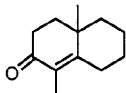
Racemic methyloctalone **3** has been used as a starting material for many transformations as well as for syntheses of racemic natural compounds. In the following examples, the absolute configuration of the methyloctalone that would be required to obtain the natural enantiomer is indicated in parentheses: β -görgonene⁷ (S), widdrol^{8,9} (R), thujopsene^{8,10} (R), (R), 7-hydroxycostal^{11,12} (R), β -selinene^{13,14}

(R), costol, costal and costic acid¹³ (R), norketoagarofuran^{15,16} (R), β -eudesmol^{13,14,15,17} (R), taxane model¹⁸ (S).

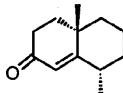
The following, chiral, key intermediates have been prepared by a procedure similar to the one described above, generally with excellent chemical and optical yields:



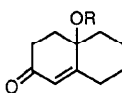
(R)^{6a,b}



5 : (R) and (S)¹⁹

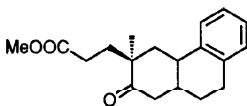


6 : (S,S)¹⁹

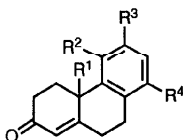


R = Me²⁰

R = CH₂Ph(R)²⁰



(R)²¹



R¹ = Me; R² = R³ = R⁴ = H (R)²¹

7: R¹ = Me; R² = OMe; R³ = H;

R⁴ = (Cl t₂)₂COOH (S)²¹

8: R¹ = Me; R² = R³ = H;

R⁴ = OMe (S)²²

9: R¹ = CH₂COO-t-Bu; R² = R⁴ = H;

R³ = OMe (S)²³

10: R¹ = Me; R² = (CH₂)₂COOMe

(R)^{6a,b}

R¹ = OMe, OCH₂Ph; R² =

(CH₂)₂COOMe²⁰

R¹ = COMe; R² = (CH₂)₂COMe²⁴

R¹ = COOEt; R² = (CH₂)₂COOEt,

CH(COO-t-Bu)₂,

(CH₂)₂COOCH₃ (R)²⁴

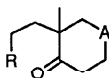


R¹ = CH₂OCH₂OMe

R² = (CH₂)₂COMe (S)^{6b}

R¹ = Me; R² = (CH₂)₂COOMe

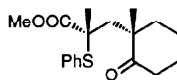
(R)^{6a,b}



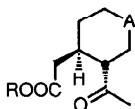
A = N-Me; R = CN (+)^{25a}

A = N-Me; R = COOMe (-)^{25a}

A = S; R = CO-Me (R and S)^{25b}

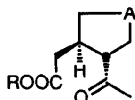


(S,S)²⁶



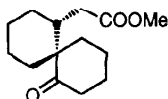
11: A = NCH₂Ph; R = Et
(R,R) and (S,S)^{27a}

12: A = CH₂; R = Me (1S,2R)²⁸

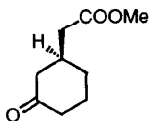


13: A = NCH₂Ph; R = Et (R,R)^{27a}

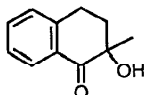
14: A = CH₂; R = Me (1S,2R)²⁸



15 : (6S,7R)²⁹



16 : (S)²⁸



17³⁰

Compounds **11-16** arise from an analogous but intramolecular reaction. A special application of the chiral imine procedure, i.e., the use of an oxaziridine rather than an electrophilic olefin, yielding compound **17**, has been reported.

Several of these optically active compounds were used for the synthesis of natural products. Thus (R)- and (S)-dimethyloctalones **5** lead, respectively, to natural and ent-geosmin,¹⁹ while another natural product was obtained from (S,S)-dimethyloctalone **6**, itself a natural compound.¹⁹ Compounds **7** and **8** were used to synthesize a ring C aromatic steroid²¹ and a key [ABC] steroid intermediate,²² respectively.

Tricyclic compound **9** is the starting compound for the preparation of a 14-hydroxyisomorphinan derivative,²³ and (R)-keto ester **10** for the preparation of (+)-cassiol³¹ and (-)-19-noraspidospermidine.³² (R,R)-**11** is an intermediate in the total synthesis of (-)-ajmalicine and (-)-tetrahydroalstonine,^{27a} as well as of (+)-yohimbine,^{27b} while its (S,S)-enantiomer can lead to (-)-(10R)-hydroxydihydroquinine.^{27a}

As in the case of methylcyclohexanone **3**, the racemic counterpart of dimethylcyclohexanone **5** has been used for the synthesis of tuberiferine³³ [the (S)-**5** enantiomer would be required for the natural compound] and for the synthesis of isocostic and 3-oxoisocostic acid³⁴ [(R)-**5** required]. From racemic **6**, both α -vetispirane³⁵ (S,S) and frullanolide³⁶ (R,R) have been synthesized.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-(-)-10-Methyl-1(9)-octal-2-one: 2(3H)-Naphthalenone,

4,4a,5,6,7,8-hexahydro-4a-methyl-, (R)- (10); (63975-59-7);

Imines 1: Benzenemethanamine, α -methyl-N-(2-methylcyclohexylidene)- (10);
(76947-33-6)

(S)-(-)- α -Methylbenzylamine: Benzylamine, α -methyl-, (S)-(-) (8);

Benzenemethanamine, α -methyl-, (S)- (9); (2627-86-3)

2-Methylcyclohexanone: Cyclohexanone, 2-methyl (8,9); (583-60-8)

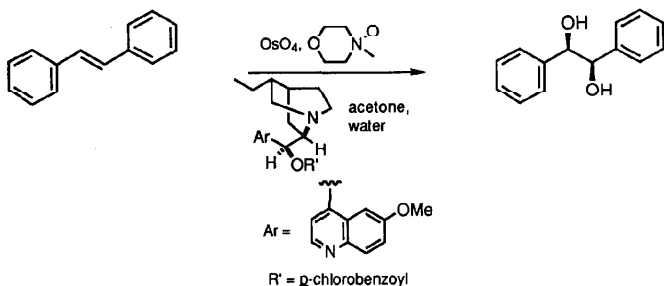
(R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone: Cyclohexanone, 2-methyl-2-(3-oxobutyl)-, (R)- (11); (91306-30-8)

Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

Imine of compound 2: 2-Butanone, 4-[1-methyl-2-[(1-phenylethyl)imino]cyclohexyl]-, [S-(R*,S*)]- (11); (94089-44-8)

(R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)

(1,2-Ethanediol, 1,2-diphenyl-[R-(R*,R*)]-)



Submitted by Blaine H. McKee,¹ Declan G. Gilheany,² and K. Barry Sharpless.¹

Checked by Aaron Balog and Robert K. Boeckman, Jr.

1. Procedure

To a 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and two glass stoppers at room temperature are added (E)-1,2-diphenylethene (trans-stilbene) (180.25 g, 1.0 mol, 1.0 equiv) (Note 1), 4-methylmorpholine N-oxide (NMO) [260 mL of a 60% by wt. aqueous solution (1.5 mol, 1.5 equiv) Notes 1 and 2], dihydroquinidine 4-chlorobenzoate (23.25 g, 0.05 mol, 0.05 equiv) (Notes 3 and 4), 375 mL of acetone and 7.5 mL water. [The solution is 0.1 M in alkaloid (Note 5), 2 M in olefin, and the solvent is 25% water/75% acetone (v/v) (Note 6)]. The flask is immersed in a 0°C cooling bath and stirred for 1 hr. Osmium tetroxide (1.0 g, 4.0 mmol, 4.0×10^{-3} equiv) is added in one portion, producing a milky brown-yellow suspension (Note 7). The reaction mixture is then stirred at 0°C for 33 hr and

monitored by silica TLC (3:1 CH₂Cl₂:Et₂O v/v) until complete. At this point, the mixture is warmed to room temperature, diluted with 500 mL of dichloromethane, and sodium metabisulfite (285 g, 1.5 mol) is added in several portions while the internal temperature is maintained at room temperature with an ice bath as needed. After addition is complete and the exothermic reaction has subsided, stirring is continued at room temperature for 1 hr (Note 8). Anhydrous sodium sulfate (50 g) is added and the mixture is stirred at room temperature overnight (Note 9). The suspension is filtered through a 20-cm Büchner funnel, the filtrand is rinsed thoroughly with acetone (3 x 250 mL), and the filtrate is concentrated to a brown paste (Note 10). The paste is dissolved in 3.5 L of ethyl acetate, transferred to a 6-L separatory funnel, and washed sequentially with water (2 x 500 mL) (Note 11), 0.25 M sulfuric acid (2 x 500 mL) (Note 12), and brine (1 x 500 mL). The initial, aqueous washes are kept separate from the subsequent acid washes which are retained for alkaloid recovery (Notes 13 and 14). The organic layer is dried (Na₂SO₄), and concentrated to give the crude diol in quantitative yield (222.7 g, 1.04 mol, 104%). The ee of the crude product is determined by ¹H NMR analysis of the derived bis-Mosher ester to be 90%. One recrystallization³ from hot aqueous 95% ethanol (3 mL/g) affords 155-162 g (72-75%) of enantiomerically pure stilbene diol as a white solid, mp 144.5-146.5°C, [α]_D²⁵ 90.0° (abs EtOH, c 1.96) (Note 15).

2. Notes

1. trans-Stilbene and N-methylmorpholine N-oxide were obtained from the Aldrich Chemical Company, Inc.

2. This solution contains 173.7 g of NMO and 117.5 mL of water. Its density is 1.130 g/mL.

3. Dihydroquinidine 4-chlorobenzoate is available from the Aldrich Chemical Company, Inc. The optical rotation of the commercial sample employed by the checkers had an $[\alpha]_D^{25}$ of -68.9° (EtOH, c 0.95).

4. Many other dihydroquinidine derivatives have been assayed in the catalytic, asymmetric dihydroxylation reaction (ADH)⁴ and the submitters have recently found that the benzoate and 2-naphthoate esters are slightly better for aryl-substituted alkenes while certain ethers are better for other substrates.⁵ However, since the level of asymmetric induction is already high, there is little advantage to be gained from their use in this case.

5. When the alkaloid concentration is increased to 0.25 M there is a slight increase in ee; when the concentration is decreased below 0.067 M there is a drastic decrease in ee.⁶

6. These solvent conditions have been optimized. The low solubility of stilbene in the reaction mixture approximates "slow addition" conditions.⁷

7. Osmium tetroxide is volatile and toxic and therefore should be used only in a well-ventilated hood. On a 1-mole scale, osmium tetroxide was added as a solid. On a smaller scale, it was added as a solution (ca. 0.5 M) in toluene.^{6a}

8. The checkers noted a significant exotherm upon addition of the sodium metabisulfite and warming to room temperature that caused the temperature of the methylene chloride solution to rise to the boiling point. Addition of the bisulfite in small portions at 0°C had no beneficial effect in moderating the exotherm that occurred after warming to room temperature.

9. This time can be reduced to 30 min without any deleterious effects.⁷

10. The filtrate is concentrated on a rotary evaporator with slight heating (bath temperature 30-40°C). In some runs with other substrates, stronger heating (bath temperature 70-80°C) caused the reaction mixture to turn black. However, there was no significant effect on either yield or enantiomeric excess in those cases.

11. These washes remove 4-methylmorpholine as well as any remaining acetone. Subsequent contact of the diol with acetone should be avoided to prevent any chance of acetonide formation.

12. It is important to use sulfuric acid at this point to ensure efficient extraction. The sulfate salt of the alkaloid is more soluble in water and less soluble in organic solvents than the hydrochloride salt. In the ADH of other alkenes the preferred system is sulfuric acid/diethyl ether. However stilbene diol is only sparingly soluble in diethyl ether, which necessitates the use of ethyl acetate. Chlorinated hydrocarbon solvents should be avoided since both alkaloid salts have appreciable solubility in them. When diethyl ether is used as the organic phase, not all of the reaction mixture dissolves in it, but the material that remains undissolved is derived solely from 4-methylmorpholine.

13. Back extraction of the acid layer yields an insignificant amount of diol in this case. However, it may be necessary for more water-soluble diols. For example, in the case of the diol from methyl 2-octenoate the yield is increased by 30% with one back extraction, while styrene glycol requires repeated prolonged extraction.

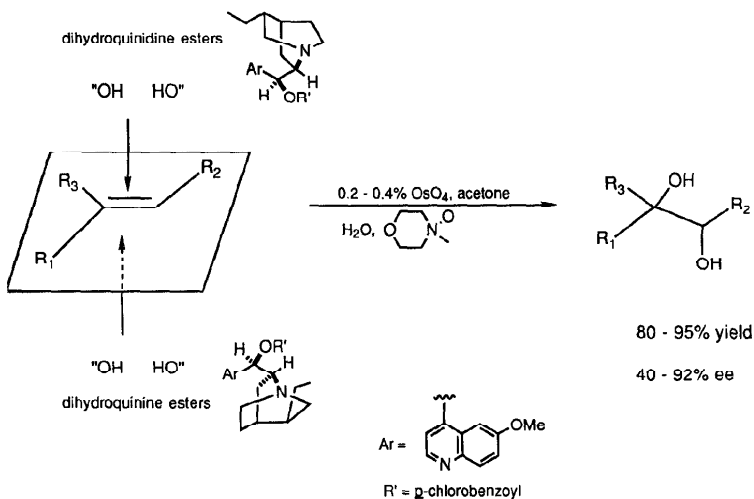
14. The alkaloid was recovered by raising the pH of the acidic washes to 11 with sodium carbonate, transferring the solution to a 6-L separatory funnel and extracting with methylene chloride (3 x 500 mL). The alkaloid was recovered in 84-85% yield as a white foam and was used without further purification in subsequent dihydroxylations. The use of recovered alkaloid by the checkers resulted in a decrease in the ee of the crude diol to 80%. The submitters, however, report ee's of 90% from repeated use of recovered alkaloid. Note that the alkaloid is stable for several days in the acidic aqueous extract. Once the solution is made alkaline, however, it should be extracted immediately.

15. Optically pure S,S-stilbene diol can be similarly obtained in 66% yield using dihydroquinine-4-chlorobenzoate. The crude ee before recrystallization is 74%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion



The present procedure describes a convenient preparation of *threo*-stilbene diol on a 1-mole scale and illustrates the utility of the catalytic, asymmetric dihydroxylation (ADH) of solid substrates on a large scale. Note that this procedure

calls for more water than initially reported.^{6a} The extra water leads to higher ee (90% cf. 78%^{6a}) by better approximating the slow addition conditions that are now almost always used for liquid olefins.^{7,8}

Recently reported uses of optically pure stilbene diol in asymmetric synthesis include. (1) the dimethyl ether as a ligand for effecting enantioselective conjugate addition;⁹ (2) the preparation of α,β -unsaturated ketals for achieving diastereoselective Simmons-Smith cyclopropanation;¹⁰ (3) the preparation of enantiomerically pure β -halohydrins;¹¹ and (4) the preparation of chiral crown ethers.¹²

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2. On leave from the Department of Chemistry. Saint Patrick's College. Maynooth, Ireland. D.G.G. acknowledges the receipt of a grant from the Irish Scholarship Exchange (Fulbright) program.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R,R)-1,2-Diphenyl-1,2-ethanediol: 1,2-Ethanediol, 1,2-diphenyl-, [R-(R*,R*)]-
(9); (52340-78-0)

(E)-1,2-Diphenylethene: Stilbene, (E)- (8); Benzene, 1,1'-(1,2-ethenediyl)bis-, (E)- (9);
(103-30-0)

4-Methylmorpholine N-oxide: Morpholine, 4-methyl-, 4-oxide (8,9); 7529-22-0)

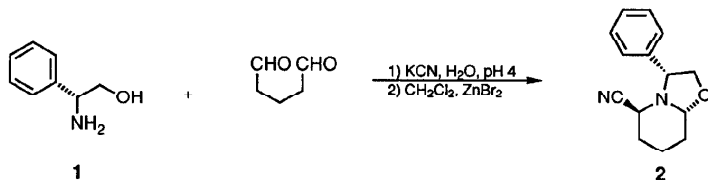
Dihydroquinidine 4-chlorobenzoate: Cinchonan-9-ol, 10,11-dihydro-6'-methoxy-,
4-chlorobenzoate (ester), (9S)- (12); (113162-02-0)

Osmium tetroxide: Osmium oxide (8); Osmium oxide, (T 4) (9); (20816-12-0)

**A STABLE CHIRAL 1,4-DIHYDROPYRIDINE EQUIVALENT FOR THE
ASYMMETRIC SYNTHESIS OF SUBSTITUTED PIPERIDINES:**

2-CYANO-6-PHENYLOXAZOLOPIPERIDINE

**(5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-,
[3R-(3 α ,5 β ,8 $\alpha\beta$)])**



Submitted by Martine Bonin, David S. Grierson, Jacques Royer, and
Henri-Philippe Husson.¹

Checked by Gilbert Rishton and Larry E. Overman.

1. Procedure

CAUTION! *Aqueous potassium cyanide is used in this procedure. All operations should be conducted in a well-ventilated hood and rubber gloves should be worn.*

2-Cyano-6-phenyloxazolopiperidine. A 2-L, round-bottomed flask is charged with 10 g (0.073 mol) of (-)-phenylglycinol (Note 1) and 40 g of citric acid in 1 L of distilled water. The mixture is stirred magnetically until complete dissolution is achieved and is cooled to 0-5°C (ice-water bath). The flask is equipped with a dropping funnel and 45 mL of an aqueous 24% glutaraldehyde solution (0.11 mol) is added dropwise over 20 min and the resultant cloudy solution is stirred for an

additional 30 min at 0°C. The cooling bath is removed and a solution of 7.15 g (0.11 mol) of potassium cyanide in 20 mL of water and 200 mL of methylene chloride are added sequentially. The resulting two-phase reaction system is stirred for 3 hr at room temperature, then the aqueous phase is neutralized (Note 2) by addition of sodium bicarbonate and the two layers are separated. The water layer is extracted with three, 200-mL portions of methylene chloride (Note 3) and the combined methylene chloride layers are dried over sodium sulfate and concentrated on a rotary evaporator to a volume of 500 mL. Zinc bromide (2 g) is added in small portions over 5 min to this solution and vigorous stirring under nitrogen is continued for 3 hr (Note 4). The reaction mixture is concentrated to a volume of approximately 150 mL (Note 5) and the resultant mixture is applied to a 10-cm diameter flash chromatography column prepared using hexane-ether (2:1) as the eluant. The desired product is eluted first (Notes 6, 7). By recrystallization from hexane, the product [10.8-11.6 g (65-70%)] is obtained analytically pure; mp 79-81°C, $[\alpha]_{\text{D}}^{23}$ -280° (CHCl₃, c 1.0) (Note 8).

2. Notes

1. The checkers used (R)-(-)-2-phenylglycinol [98%, $[\alpha]_{\text{D}}^{24}$ -31.7° (1 N HCl, c 0.76)] purchased from Aldrich Chemical Company, Inc. The submitters employed material [mp 78°C, $[\alpha]_{\text{D}}^{20}$ -26.5° (MeOH, c 0.7)] prepared by lithium aluminum hydride reduction of (-)-phenylglycine and report that the yield of 2-cyano-6-phenyloxazolopiperidine prepared from this material is 75-83%.

2. Extraction at pH greater than 9 led to the formation of by-products (2,6-dicyanopiperidines)² and consequently to a lower yield of the desired product.

3. The aqueous layer containing residual potassium cyanide is destroyed by addition of potassium permanganate.

4. The reaction must be carried out in a well-ventilated hood as hydrogen cyanide may be evolved.

5. Complete evaporation of the solvent gives a viscous oil which is only slightly soluble in either the elution solvent or methylene chloride. Significant loss of material thus occurs during the purification process.

6. $R_f = 0.6$ (SiO_2 , hexane-ether : 2-1) for the product.

7. Further elution permits the isolation of a mixture of two other isomers (0.3 g, 3.6%).

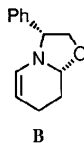
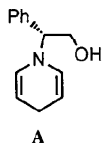
8. The product obtained by this procedure shows the following spectral data: IR (CHCl_3) cm^{-1} : 2100; ^1H NMR (400 MHz, CDCl_3) δ : 1.5-2.0 (m, 5 H); 2.13 (dd, 1 H, $J = 11.5$, $J' = 1.5$); 3.74 (t, 1 H, $J = 7.8$); 3.85 (bd, 1 H, $J = 7.1$); 3.90 (t, 1 H, $J = 8.0$); 4.12 (dd, 1 H, $J = 9.7$, $J' = 2.8$); 4.25 (t, 1 H, $J = 7.9$); 7.4 (m, 5 H); ^{13}C NMR (CDCl_3 , 15 MHz) δ : 19.3; 28.0; 30.0; 47.4; 63.9; 73.0; 89.9; 116, 128.2, 128.6; 129.0; 137.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

The preparation described here is an improvement of the previous procedure.³ The double condensation of glutaraldehyde with the amino group of (R)-(-)-phenylglycinol (related to the Robinson-Schöpf condensation) probably leads to the expected product via the formation of an intermediate of type A⁴ and/or B.

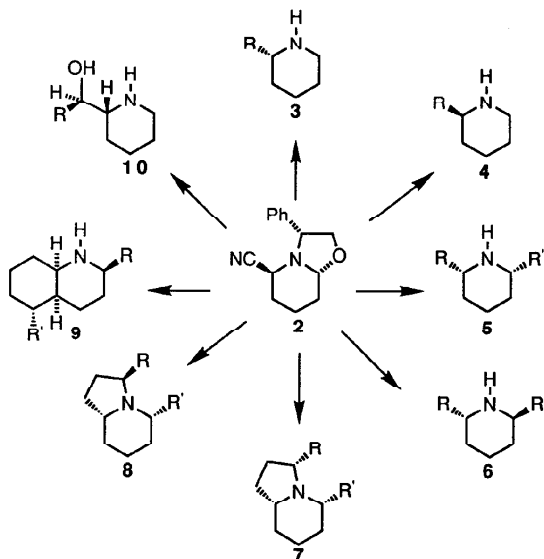


Trapping intermediate **B** with cyanide ion would lead to the final product. Formation of the four possible product isomers has been observed after short reaction periods, and equilibration of this mixture to the described product **2** has been demonstrated. In the original procedure compound **2** was obtained in 50-60% yield after prolonged (72 hr) reaction of the reactants in water. In the present procedure equilibration of all intermediates and/or product isomers to the observed, thermodynamically more stable form of compound **2** is accelerated and the yield improved considerably through the use of zinc bromide as a catalyst in an organic medium.

2-Cyano-6-phenyloxazolopiperidine, **2**, is a stable, chiral, 1,4-dihydropyridine equivalent, useful for the asymmetric synthesis of piperidines. When synthon **2** was used, the asymmetric syntheses of several alkaloids or analogs have been achieved and reported in the literature. A sequence of reactions involving alkylation at the α -aminonitrile center (LDA, RX), elimination of the cyano group with concomitant opening of the oxazolidine ring (NaBH_4), and finally debenzoylation (H_2 , Pd/C) permits the preparation of α -alkylated piperidine **3** in both high yield (90% overall) and ee ($\geq 95\%$).⁵ If one starts from the same compound **2**, enantiomeric **4** can also be prepared.⁵ A regio- and chemoselective elimination of the cyano group is also possible giving an oxazolopiperidine intermediate which can further be used to prepare the cis- and trans-2,6-disubstituted piperidines **5**⁵ and **6**.⁶ When the appropriate electrophile is used, enantioselective syntheses of indolizidines **7**,³ **8**,⁷ decahydroquinolines **9**,⁸ and amino alcohol **10**⁹ have been achieved.

The asymmetric syntheses of β -amino alcohols have also been reported recently in the literature^{10,11} using chiral compound **2** as a starting material.

Scheme



1. Institut de Chimie des Substances Naturelles du C.N.R.S., 91198 Gif-sur-Yvette Cedex, France.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

2-Cyano-6-phenyloxazolopiperidine: 5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-, [3R-(3 α ,5 β ,8a β)]- (11); (88056-92-2)

Potassium cyanide (8,9); (151-50-8)

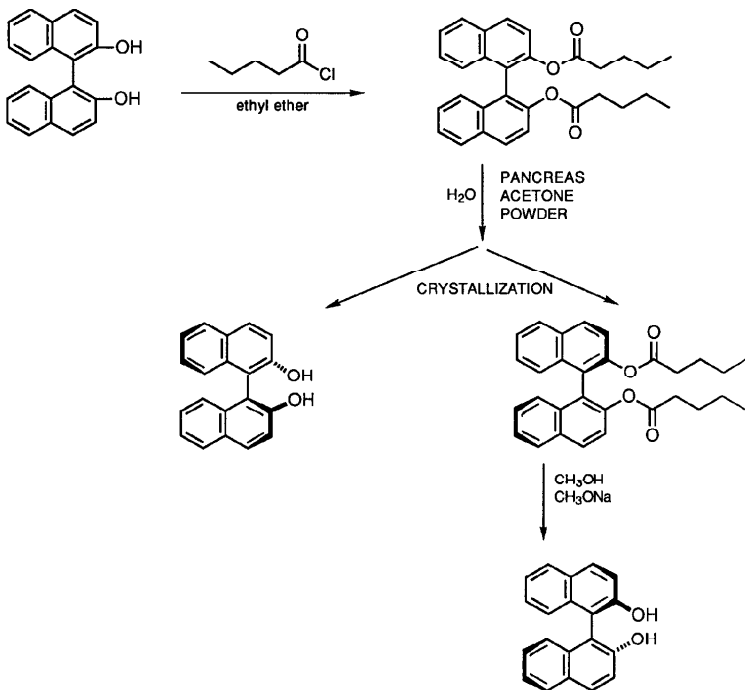
(-)-Phenylglycinol: Benzeneethanol, β -amino-, (R)- (9); (56613-80-0)

Citric acid (8); 1,2,3-Propanetricarboxylic acid, 2-hydroxy- (9); (77-92-9)

Glutaraldehyde (8); Pentanedial (90); (111-30-8)

Zinc bromide (8,9); (7699-45-8)

(S)-(-)- AND (R)-(+)-1,1'-BI-2-NAPHTHOL
([1,1'-Binaphthalene]-2,2'-diol, (S)- and
[1,1'-Binaphthalene]-2,2'-diol, (R)-)



Submitted by Romas J. Kazlauskas.¹

Checked by Mark R. Sivik and Leo A. Paquette.

1. Procedure

A. Racemic 1,1'-bi-2-naphthyl pentanoate. A suspension of 203 g (0.71 mol) of racemic 1,1'-bi-2-naphthol (Note 1) and 215 mL (1.54 mol) of triethylamine in 2 L of ethyl ether is stirred magnetically in a 4-L Erlenmeyer flask. Over a period of 20 min 185 mL (1.56 mol) of pentanoyl chloride is added (Note 2) and the suspension is stirred for an additional hour to ensure complete reaction (Note 3). The mixture is poured into a 6-L separatory funnel and washed twice with 2-L portions of aqueous 1 M sodium bicarbonate and once with a 2-L portion of water resulting in a clear yellow-orange ether solution.

B. (S)-(-)-1,1'-Bi-2-naphthol. In a 12-L, round-bottomed flask the above ether solution is diluted to 4 L with additional ethyl ether. A 5.0-mL aliquot of this solution is used to assay the enzyme (Note 4). The remaining ether solution is stirred using an overhead stirrer with 4 L of aqueous 0.1 M phosphate buffer (pH 7.5) containing 60 g of crude sodium taurocholate (Note 5). An opaque emulsion forms. The reaction is started by adding 2000 units of cholesterol esterase activity (100-150 g of bovine pancreas acetone powder, Note 4). *Stirring is continued at ~25°C and the flask is stoppered to minimize evaporation of ether.* The pH of the emulsion is measured occasionally and readjusted to 7.2 ± 0.3 by adding aqueous 1 M sodium hydroxide. Approximately 250 mL of base is consumed during the first 3 hr; an additional 400 mL is consumed over the next 20 hr. Although the consumption of base virtually ceases after 24 hr stirring is continued for a total of 3 days (Note 6).

To break the emulsion 400 mL of ethanol is added and the mixture is transferred to separatory funnels and allowed to settle for 4 hr. Three layers form: at the top - a clear yellow ether phase, at the bottom - a brown aqueous phase and in between - an opaque emulsion layer. The brown aqueous layer is discarded. The emulsion layer (~1 L) is transferred to a flask and broken up by addition of 200 g of

magnesium sulfate in portions. Heat is evolved, the ether boils and two layers form. This ether layer is combined with the first ether layer, dried over ~50 g of magnesium sulfate, filtered and concentrated by rotary evaporation to ~300 mL of an orange oil. Toluene (500 mL) is added and the solution cooled to 4°C overnight. The fine white crystals (70-71 g) are collected by filtration and washed twice with 20-mL portions of cold toluene (Note 7). The filtrate is concentrated to ~600 mL by rotary evaporation and cooled once again to 4°C. The additional 10 g of crystals which form are collected by filtration and washed twice with 20-mL portions of toluene. Recrystallization of the combined crystals from 375-400 mL of toluene yields 65-68 g (64-67%) of white crystals, mp 211-213.5°C; $[\alpha]_D^{19} -33.2 \pm 0.8^\circ$ (THF, c 0.2); >99% diol (see Note 3), >99.9% enantiomeric purity (Note 8).

C. *(R)-(+)-1,1'-Bi-2-naphthol*. Toluene In the above filtrate is removed by rotary evaporation, and the residue is recrystallized from methanol (500 ml) overnight at 4°C. Yellow crystals (125-141 g) form and are collected by filtration and washed twice with 20 mL of hexane. Recrystallization from 500 mL of methanol yields pure (R)-binaphthol dipentanoate [mp 63-65°C, 89-102 g, >99% ee (R), $[\alpha]_D^{19} +15.0 \pm 0.3^\circ$ (CHCl₃, c 0.4), Note 9]. If desired, an additional 25 g of dipentanoate can be isolated from the filtrate by column chromatography on 1 kg of silica gel eluted with methylene chloride followed by crystallization (Note 9).

The crystalline dipentanoate (89-102 g, 0.20 mol) is dissolved in 1 L of methanol containing 6.6 g (0.12 mol) of sodium methoxide. After 4 hr at room temperature, analysis of the solution by thin layer chromatography (Note 3) shows only traces of the mono- and diester. The solution is neutralized to pH <7 (test paper) with ~10 mL of concd hydrochloric acid. The solution is diluted with 1 L of 0.1 M phosphate buffer (pH 7), transferred to a 4-L separatory funnel and extracted with a mixture of 1 L of ethyl ether and 500 mL of toluene. The organic layer is washed with a 1-L portion of water, dried over magnesium sulfate, concentrated to 300 mL and cooled to 4°C.

White crystals (48-64 g) separate and are collected by filtration and washed twice with 20-mL portions of cold toluene, mp 211-213.5°C; $[\alpha]_D^{19} +33.9 \pm 0.2^\circ$ (THF, c 0.2); 99% chemical purity (Note 3), >99% enantiomeric purity (Note 8).

2. Notes

1. (\pm)-1,1'-Bi-2-naphthol was purchased from Aldrich Chemical Company, Inc. or prepared by oxidative coupling of 2-naphthol.²

2. The initial suspension is thick and can sometimes be difficult to stir magnetically. In this case, occasional swirling by hand is sufficient. The mixture thins as the reaction proceeds. *Caution: This exothermic reaction causes the ether to boil; pentanoyl chloride should be added slowly, allowing the heat of reaction to dissipate.* The checkers cooled the reaction mixture in an ice bath during addition of the acid chloride. Pentanoyl chloride was obtained from Aldrich Chemical Company, Inc.

3. To ensure high enantiomeric purity of the product there should be <0.5% 1,1'-bi-2-naphthol or its monoester in this solution. The relative amounts of binaphthol species can be accurately determined by HPLC on a reverse-phase column eluted with a water-acetonitrile gradient (50-100% over 10 min). Both 1,1'-bi-2-naphthol and its dipentanoate have equal (within 2%) extinction coefficients at 254 nm. The monopentanoate absorbs more strongly: the relative extinction coefficient at 254 nm is 1.13. Alternatively, the solution composition can be estimated using thin layer chromatography: silica gel eluted with 1:4 ethyl acetate/cyclohexane: 1,1'-bi-2-naphthol, R_f 0.39; monopentanoate, R_f 0.56; dipentanoate, R_f 0.71.

4. The catalyst for this reaction is the enzyme cholesterol esterase (EC 3.1.1.13) Bovine pancreas acetone powder (Sigma Chemical Company), a crude extract from pancreas, is an inexpensive source of cholesterol esterase activity. This extract contains ~15 units of cholesterol esterase activity/gram; unit = μ mol of ester

hydrolyzed/min. To measure the activity, the ethereal aliquot of binaphthol dipentanoate is stirred rapidly using a magnetic stirrer with 5.0 mL of 10 mM phosphate buffer (pH 7.0) containing 75 mg of crude sodium taurocholate (Sigma Chemical Company). Approximately 200 mg of acetone powder is added and the pH of the emulsion is monitored with a pH meter and maintained at 7.0 by addition of aqueous 0.1 M sodium hydroxide in portions of 50 μ L until ~200 μ L has been added, ~70 min. The slope of a plot of μ moles of base consumed vs. time gives the activity of the acetone powder. (The amount of base needed to readjust the pH to 7.0 after the addition of the slightly acidic acetone powder is ignored in the activity calculation.)

5. Directions for the preparation of this buffer solution are given in reference 3.

6. After 24 hr, analysis by HPLC shows 37% binaphthol, 10% monopentanoate and 53% dipentanoate, after an additional 2 days of stirring, analysis shows 45%, 3%, and 52%. Isolation of binaphthol and diester by crystallization is substantially more difficult and less efficient from reaction mixtures containing <40 mol % binaphthol.

7. Binaphthol may not crystallize if the solution is wet. If no crystals form, water can be removed by rotary evaporation of the water-toluene azeotrope.

8. Enantiomeric purity of binaphthol is determined using chiral stationary phase HPLC: Pirkle Type 1-A column (Regis Chemical Company) eluted with 20:1 hexane/2-propanol⁴ or poly(triphenylmethyl)methacrylate on silica gel (Chiralpak OT, Daicel Chemical Industries, LTD) eluted with methanol.⁵ To determine enantiomeric purities >99% ee an HPLC trace of the unknown is compared to the HPLC trace of unknown containing 0.2% deliberately-added racemic material.

9. Crystallization of (R)-binaphthyl dipentanoate increases its enantiomeric purity from ~92% ee in the reaction mixture to >99% ee. The enantiomeric purity of the final product, binaphthol, is not increased by crystallization. The recrystallization step for the dipentanoate ensures high enantiomeric purity. Usually crystallization from methanol must be induced by scratching the side of the flask with a glass rod.

The enantiomeric purity of the dipentanoate is determined after cleavage to binaphthol. A sample of dipentanoate is treated with an equivalent of sodium methoxide in methanol. After 30 min the solution is neutralized with excess acetic acid and analyzed by HPLC as in Note 8.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Enantiomerically pure binaphthol is used as a chiral auxiliary.⁶ For example, it has been used to prepare chiral aluminum hydride reducing agents,⁷ chiral Lewis acids catalysts,⁸ and chiral crown ethers.⁹

The best previous resolution of binaphthol uses fractional crystallization of the diastereomeric cinchonine salts of binaphthol cyclic phosphate ester.¹⁰ The resolution using cholesterol esterase involves fewer manipulations and thus is simpler and faster than the cinchonine method. Fewer manipulations also enable the resolutions using cholesterol esterase to be carried out on a larger scale. The high enantioselectivity of cholesterol esterase assures high ee for the (S)-enantiomer, while crystallization of (R)-binaphthyl dipentanoate assures high enantiomeric purity for the (R)-enantiomer.

Octahydrobinaphthol and several spirobiindanolols can also be resolved using this method, but several bromo-substituted binaphthols could not be resolved because their esters were not hydrolyzed.¹¹

1. Department of Chemistry, McGill University, 801 Sherbrooke St., W., Montreal, PQ H3A 2K6 Canada. Initial work was done at General Electric Company, Corporate Research and Development, Schenectady, NY.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(-)-1,1'-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol, (S)-(-)- (8);

[1,1'-Binaphthalene]-2,2'-diol, (S)- (9); (18531-99-2)

(R)-(+)-1,1'-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol, (R)-(+)- (8);

[1,1'-Binaphthalene]-2,2'-diol, (R)- (9); (18531-94-7)

(±)-1,1'-Bi-2-naphthyl pentanoate: Pentanoic acid, [1,1'-binaphthalene]-2,2'-diyl ester,

(±)- (12); (100465-51-8)

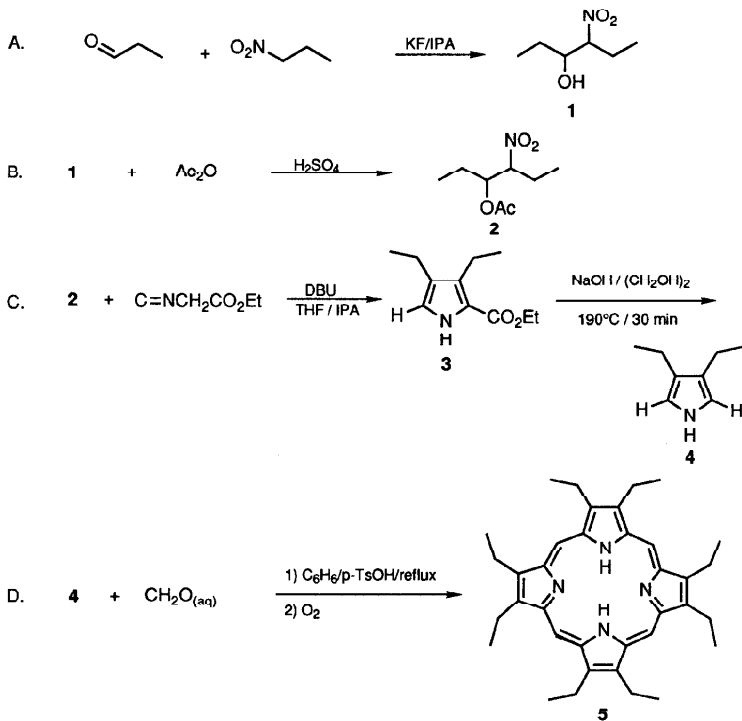
(±)-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol, (±)- (9); (41024-90-2)

Pentanoyl chloride (8,9); (638-29-9)

(R)-1,1'-Bi-2-naphthyl pentanoate: Pentanoic acid, [1,1'-binaphthalene]-2,2'-diyl ester,

(R)- (12); (110902-38-0)

**3,4-DIETHYLPYRROLE AND 2,3,7,8,12,13,17,18-
OCTAETHYLPORPHYRIN**
(21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl-)



Submitted by Jonathan L. Sessler,¹ Azadeh Mozaffari, and Martin R. Johnson.

Checked by Jürgen Fischer and Ekkehard Winterfeldt.

1. Procedure

*A. 4-Nitro-3-hexanol (1).*² To a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, dropping funnel, and drying tube are added propionaldehyde (174 g, 3 mol) and isopropyl alcohol (IPA) (450 mL) (Note 1). The solution is stirred while finely ground potassium fluoride (25 g, 0.15 mol) is added to the flask. 1-Nitropropane (267.3 g, 3 mol) (Note 1) is then added dropwise with stirring, and the temperature is kept below 40°C with the aid of an ice bath (Note 2). The ice bath is removed about 30 min after the addition of 1-nitropropane is complete. The flask contents are stirred for an additional 18 hr. The catalyst is then removed by filtration and the filtrate is concentrated under reduced pressure. The residue is poured into water (500 mL) and the oil is extracted with ether (3 x 300 mL). The ethereal layer is dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent is removed under reduced pressure. The remaining liquid is distilled under reduced pressure and the fraction boiling at 88-90°C/2 mm is collected in a tared, 1-L round-bottomed flask, yielding 3-nitro-4-hexanol (330 g, 2.24 mol, 65%) (Note 3). The flask containing the product is used directly in the next step.

*B. 4-Acetoxy-3-nitrohexane (2).*³ To the above flask, containing 3-nitro-4-hexanol (330 g, 2.24 mol), is added a magnetic stirring egg and 1 mL of concd sulfuric acid. The contents of the flask are stirred in an ice bath and acetic anhydride (240 g, 2.35 mol) is added in portions, keeping the temperature of the reactants below 60°C. After the addition of the acetic anhydride is complete, the contents of the flask are stirred for 1 hr. The flask is then equipped for vacuum distillation. The lower boiling components (Ac_2O and AcOH) are removed at 25 mm by gently heating the stirred contents of the flask ($\leq 100^\circ\text{C}$ bath temperature). After these reagents have been removed, the system is cooled, attached to a vacuum pump, and carefully heated. The

fraction boiling at 105-107°C/10 mm is collected, affording 4-acetoxy-3-nitrohexane (379 g, 2.0 mol, 90%) (Note 4).

C. *Ethyl 3,4-diethylpyrrole-2-carboxylate* (3)⁴ and *3,4-Diethylpyrrole* (4). A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, dropping funnel, thermometer, and drying tube, and charged with 3-acetoxy-2-nitrohexane (103 g, 0.54 mol), ethyl isocynoacetate (50.7 g, 0.45 mol, Note 5), anhydrous tetrahydrofuran (320 mL), and anhydrous isopropyl alcohol (IPA) (130 mL) (Note 1). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 152 g, 1 mol) (Notes 6 & 7) is then added, taking care to maintain the temperature at 20°C to 30°C at all times with the aid of an ice bath (Note 8). When addition of DBU is complete, the orange solution is stirred for 4 hr at room temperature. The solvent is completely removed under reduced pressure (50°C bath temp, 20-40 mm) and the residue is poured into a 1-l beaker and diluted with warm water (300 ml). To this biphasic mixture is added diethyl ether (300 mL). The contents of the beaker are poured into a separatory funnel. The aqueous layer is drawn off and extracted with an additional two portions of ether (300 mL). The ether layers are combined and washed with aqueous 10% hydrochloric acid (2 x 300 mL) and dried over magnesium sulfate (MgSO₄). The ether is removed under reduced pressure in a 1-L round-bottomed flask, leaving approximately 95 g of crude ethyl 3,4-diethylpyrrole-2-carboxylate (3) (Note 7). This material is not isolated, but is decarboxylated directly as follows: To the crude product 3 (95 g) is added sodium hydroxide (30 g, 0.75 mol) and ethylene glycol (300 mL). The contents are held at reflux under nitrogen for 1 hr, cooled, transferred to a 2-L separatory funnel, and diluted with water (500 mL) and hexane (600 mL). The layers are separated, and the aqueous layer is extracted further with hexane (3 x 300 mL). The hexane layers are combined, dried over MgSO₄, and concentrated under reduced pressure. The residue is distilled under reduced pressure, and the fraction boiling at

100°C/25 mm is collected, yielding 3,4-diethylpyrrole (21.14-22.00 g, 0.17-0.177 mol, 38.1-40%) (Note 9).

D. 2,3,7,8,12,13,17,18-Octaethylporphyrin (5). A 500-mL, round-bottomed flask is wrapped with aluminum foil and equipped with a reflux condenser with a Dean-Stark trap, mechanical stirrer, and nitrogen inlet. The flask is charged with 3,4-diethylpyrrole (1 g, 8.1 mmol), benzene (300 mL) (Note 10), a 37% solution of aqueous formaldehyde (0.73 mL, 8.9 mmol), and *p*-toluenesulfonic acid (0.03 g, 1.7 mmol). The mixture is stirred and heated at reflux under nitrogen using an oil bath, and the water is removed by means of the Dean-Stark trap. After 8 hr, the solution is cooled, and the Dean-Stark trap and condenser are replaced with a fritted glass aerator/bubbler. Oxygen is bubbled through the brown mixture while it is stirred for 12-24 hr. Benzene is removed from the flask by distillation under reduced pressure, and the residue is dissolved in chloroform (20 mL) (Note 11). The solution is washed with 1 N sodium hydroxide (40 mL) and water (2 x 20 mL). The chloroform solution is concentrated to 5 mL in a 100-mL, round-bottomed flask, carefully layered over with methanol (≈70 mL), and allowed to stand for 48 hr. The resulting solid is collected by filtration and dried under reduced pressure for 24 hr. The crude material is recrystallized twice from chloroform-hexanes [effected by dissolving in chloroform (≈10 mL), layering over with hexanes (≈70 mL), and allowing to stand overnight]. The final precipitate is collected by filtration and dried under reduced pressure for 48 hr to yield analytically pure 2,3,7,8,12,13,17,18-octaethylporphyrin (720 mg, 1.34 mmol, 66.4%) as a purple, amorphous powder (Note 12).

2. Notes

1. Propionaldehyde and 1-nitropropane were obtained from Aldrich Chemical Company, Inc., and used as received. Isopropyl alcohol and tetrahydrofuran were obtained from J.T. Baker and used as received.

2. It is necessary to cool the reaction vessel to prevent the volatile propionaldehyde from evaporating.

3. The literature boiling point is reported² as 89°C (2 mm).

4. The spectral and analytical properties are as follows: ¹H NMR (CDCl₃, 300 MHz) δ: 0.99 (m, 6 H, CH₃), 1.62 and 1.80 (2 x m, 2 H, O₂NCHCH₂CH₃), 1.99 and 2.12 (2 x m, 2 H, CH₃CO₂CHCH₂CH₃), 2.06 (m, 3 H, CH₃CO₂), 4.56 (m, 1 H, CHNO₂), 5.16 and 5.24 (2 x m, 1 H, CH₃CO₂CH); C.I. MS, (M+1)⁺ 190 (calcd for C₈H₁₅NO₄·H: 190). Anal. Calcd for C₈H₁₅NO₄: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.98; H, 8.14; N, 7.01.

5. A disadvantage of the present procedure is that it requires the use of the relatively foul-smelling substance, ethyl isocyanoacetate. Although this material is commercially available (from, e.g., Aldrich Chemical Company, Inc.), it is moderately expensive. The authors have found that the existing preparative procedure (Hartman, G. D.; Weinstock, L. M. *Org. Synth., Coll. Vol VI 1988*, 620) can be improved by the use of trichloromethyl chloroformate (Kurita, K.; Iwakura, Y. *Org. Synth., Coll. Vol. VI 1988*, 715) rather than phosphoryl chloride. This substitution simplifies purification of the isocyanoacetate by eliminating the aqueous portion of the workup.

6. DBU was obtained from Aldrich Chemical Company, Inc. and used as received.

7. Two equivalents of DBU are used here. One equivalent of DBU eliminates acetate from one of the reactants to form 3-nitro-3-hexene in situ, which goes on to form the pyrrole. The intermediate ethyl 3,4-diethylpyrrole-2-carboxylate can also be

prepared directly from ethyl isocynoacetate and 3-nitro-3-hexene in good yield (86%) under conditions similar to those outlined here.⁵ Although this alternative requires a further manipulative step, it requires only half as much DBU.

8. It is important not to allow the temperature to drop below 20°C because the reaction slows down considerably. Unreacted DBU then builds up. As a result, when the temperature does climb, it does so rapidly (often to as high as 65°C). This results in a significantly lower yield.

9. The spectral and physical properties are as follows: ¹H NMR (CDCl₃, 300 MHz) δ: 1.16 (t, 6 H, CH₂CH₃), 2.47 (q, 4 H, CH₂CH₃), 6.42 (d, 2 H, pyrrole CH), 7.65 (s, 1 H, pyrrole NH); MS m/e (relative intensity) 123 (46), 108 (100), 93 (37); bp 100°C/25 mm; 69°C/7 mm (lit.⁶ bp, 83°C/10 mm).

10. Benzene is a known carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.

11. Chloroform is a suspected carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.

12. The spectral and analytical properties are as follows: ¹H NMR (CDCl₃, 300 MHz) δ: -3.72 (s, 2 H, NH), 1.95 (t, 24 H, CH₂CH₃), 4.12 (q, 16 H, CH₂CH₃), 10.12 (s, 4 H, meso CH); HRMS, M⁺ 534.37351 (calcd for C₃₆H₄₆N₄: 534.37225). Anal. Calcd for C₃₆H₄₆N₄: C, 80.85; H, 8.67; N, 10.48. Found: C, 80.89; H, 8.56; N, 10.37; UV-vis (CHCl₃-MeOH 95:5 vv.) λ_{max} (log ε): 398 (5.20), 498 (4.10), 533 (4.00), 565 (3.79), 618 (3.68) nm.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Octaethylporphyrin (OEP) and tetraphenylporphyrin (TPP) remain among the most widely used of an increasingly diverse set of available synthetic porphyrins. The inherently high symmetry and relatively good solubility properties of these systems often combine to make them the models of choice for a wide range of biological modeling and inorganic chemical applications.⁷ Recently, an optimized synthesis of TPP and related tetraarylporphyrins has been developed by Lindsey and co-workers.⁸ At present, however, the synthesis of OEP (5) remains problematic: Although numerous strategies have been reported,^{5,9-14,15} no convenient, high-yield procedure currently exists.

Traditionally, octaethylporphyrin has been prepared by the self-condensation of 2-N,N'-diethylaminomethyl-3,4-diethylpyrrole,^{9,10} ethyl 5-N,N'-diethylaminomethyl-3,4-diethylpyrrole-2-carboxylate,^{11,12} or 3,4-diethyl-5-hydroxymethylpyrrole-2-carboxylic acid under oxidative conditions.¹³ It has also been prepared on a small scale directly from 3,4-diethylpyrrole in 65% yield by condensation with aqueous formaldehyde under acid-catalyzed conditions,¹⁴ using conditions similar to those which have proved useful for preparing the corresponding octamethylporphyrin analogue.¹⁶ All of these syntheses derive from the same, initial pyrrole precursor, namely, ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate, prepared from the classic, reverse-sense Knorr reaction of ethyl propionylacetate with 2,4-pentanedione, and they require several steps before the ultimate porphyrin-forming condensation. Octaethylporphyrin has also been prepared recently by the reduction of 2,8,12,18-tetraacetyl-3,7,13,17-tetraethylporphyrin by diborane,¹⁴ and by the condensation of 3,4-diethylpyrrole-N-carboxylic acid with formaldehyde in refluxing acetic acid/pyridine.¹⁵ Neither of these procedures, however, truly overcomes the problem associated with preparing the initial pyrrole.

The synthesis reported here circumvents many of the problems associated with existing preparative methods. Specifically, it makes use of a new procedure of Barton and Zard⁴ in the key pyrrole-forming step. This method, which gives an α -unsubstituted pyrrole ester (e.g., **3**) directly in good yield, provides a substantial saving in labor when compared to the Knorr approach, and it is very flexible with regard to the kinds of β -substitution allowed. Since the remaining α -ester group can be conveniently removed by saponification and subsequent decarboxylation (often, as is the case here, without isolation of the initial pyrrole product), this method provides a quick and easy means of preparing 3,4-dialkylated pyrroles. Simple acid-catalyzed condensation of the resulting 3,4-dialkylpyrroles with formaldehyde and subsequent oxidation is then all that is required to complete the synthesis of an octaalkylporphyrin.^{17,18} We have found that these latter transformations may be readily effected using aqueous formaldehyde under acid-catalyzed dehydrating conditions, followed by simple air-induced oxidation. In the specific case of octaethylporphyrin, when the reaction is run on a 1-g scale, a 75% yield of analytically pure product is obtained following workup and purification (which involves only simple recrystallizations and no chromatographic separations). This procedure can be conveniently scaled up by a factor of ten. Under these conditions, it still gives a good yield (55%) of pure product. It does, however, require relatively large amounts of benzene (3 L for a reaction carried out with 10 g of 3,4-diethylpyrrole), which could present a health hazard. However, if due caution is exercised with regard to this point, the present method provides an easy way to prepare large quantities of octaethylporphyrin. As such it represents a considerable advance over earlier methods in terms of both ease and convenience.

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17. Alternatively, the ethyl 3,4-diethylpyrrole-2-carboxylate may be carried on directly to give octaethylporphyrin,⁵ although the yields reported (ca. 40%) are not quite as good as those obtained by the present procedure. Similarly, this substance or the 3,4-diethylpyrrole produced by the present procedure could conceivably serve as the basis for an improved synthesis via a Mannich base-type approach such as that outlined in refs. 9-12.
18. The procedure reported here appears to be quite general. We have, for example, used it to prepare a β -substituted tetrakis-fused cyclohexylporphyrin (1,2,3,4,8,9,10,11,15,16,17,18,22, 23,24,25-hexadecahydro-29H,31H-tetra-benzo[BGLQ]porphine) in 51% overall yield starting from 1-nitrocyclohexene.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,4-Diethylpyrrole: Pyrrole, 3,4-diethyl- (8,9); (16200-52-5)

2,3,7,8,12,13,17,18-Octaethylporphyrin: Porphine, 2,3,7,8,12,13,17,18-octaethyl- (8);

21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl- (9); (2683-82-1)

4-Nitro-3-hexanol: 3-Hexanol, 3-nitro- (8,9); (5342-71-2)

Propionaldehyde (8); Propanal (9); (123-38-6)

1-Nitropropane: Propane, 1-nitro- (8,9); (108-03-2)

4-Acetoxy-3-nitrohexane: 3-Hexanol, 4-nitro-, acetate (9); (3750-83-2)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

Ethyl 3,4-diethylpyrrole-2-carboxylate: 1H-Pyrrole-2-carboxylic acid,

3,4-diethyl-, ethyl ester (11); (97336-41-9)

Ethyl isocyanoacetate: Acetic acid, isocyano-, ethyl ester (8,9); (2999-46-4)

1,8-Diazabicyclo[5.4.0]undec-7-ene: Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro- (8,9); (6674-22-2)

Formaldehyde (8,9); (50-00-0)

p-Toluenesulfonic acid (8); Benzenesulfonic acid, 4-methyl- (9); (6102-52-5)

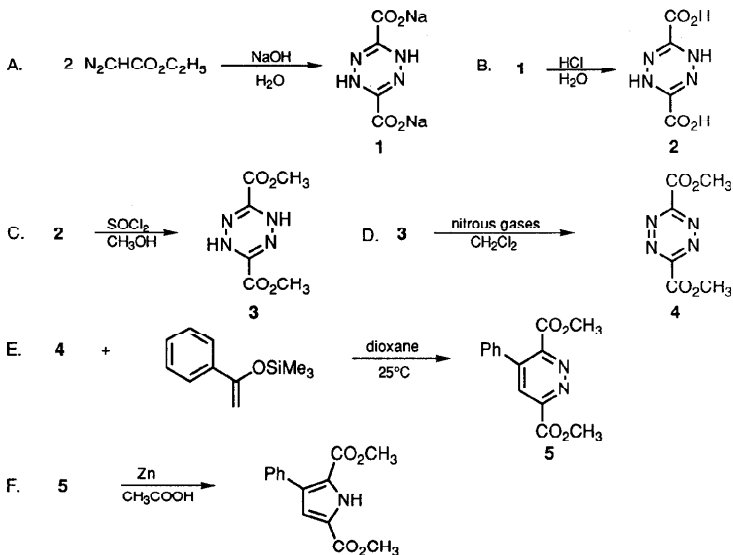
Trichloromethyl chloroformate: Formic acid, chloro-, trichloromethyl ester (8);

Carbonochloridic acid, trichloromethyl ester (9); (503-38-8)

**PREPARATION AND DIELS-ALDER REACTION OF A REACTIVE,
ELECTRON-DEFICIENT HETEROCYCLIC AZADIENE: DIMETHYL 1,2,4,5-
TETRAZINE-3,6-DICARBOXYLATE. 1,2-DIAZINE AND PYRROLE**

INTRODUCTION

1,2,4,5-Tetrazine-3,6-dicarboxylic acid, dimethyl ester)



Submitted by Dale L. Boger, James S. Panek, and Mona Patel.¹

Checked by Richard Hutchings and Albert I. Meyers.

1. Procedure²

A. Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate. A 2-L, three-necked, round-bottomed flask is equipped with an overhead stirrer, thermometer, and a 500-mL addition funnel. Sodium hydroxide (320 g, 8 mol) and 500 mL of water are added. Ethyl diazoacetate (200 g, 1.75 mol, Note 1) is placed in the addition funnel and added dropwise to the stirred sodium hydroxide solution so as to maintain the temperature of the reaction mixture between 60°C and 80°C (approximately 1.5 hr, Note 2). After the reaction slurry is cooled to room temperature, it is poured into 2 L of 95% ethanol, mixed well, and the liquid is decanted. This washing procedure is repeated five times using 1.5 L of 95% ethanol each time. The precipitate is collected by filtration using a Büchner funnel, the collected solid is washed with 1 L of absolute ethanol and 1 L of ether, and dried (12 hr) in the air to afford 160-184 g (85-97%) of disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate as yellow brown solid.

B. Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid. A 2-L, three-necked, round-bottomed flask is equipped with an overhead stirrer and a 100-mL addition funnel. Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (90.37 g 0.42 mol) in 100 mL of water and 100 g of crushed ice are added. The resulting slurry is cooled with an ice/sodium chloride bath and a solution of concentrated hydrochloric acid (84 mL of 36-38%) is added dropwise with stirring over 45 min. The reaction mixture is washed five times with 200 mL of dry ether and the ether layer is decanted. The product is immediately collected by filtration using a Büchner funnel. Drying the collected solid at room temperature under reduced pressure affords 51.6-53.06 g (72-74%) of dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid as a yellow powder: mp 144-148°C (Note 3).

C. Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate. Absolute methanol (700 mL, Note 4) is placed in a dry, 2-L, round-bottomed flask fitted with an overhead stirrer, thermometer, and a 100-mL addition funnel and is cooled to -30°C. Thionyl

chloride (62.12 g, 0.522 mol, 38.1 mL, Note 5) is added carefully with stirring and the reaction mixture is allowed to stir at -30°C for 30 min. Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (45.00 g, 0.261 mol) is added as a solid in portions over 30 min to the cooled, stirred thionyl chloride-methanol solution (Note 6). The reaction mixture is allowed to warm to room temperature (1 hr) and is subsequently warmed to 35-40°C (internal temperature) for 2 hr. The reaction mixture is cooled to -30°C and the precipitate is collected by filtration using a Büchner funnel. The collected solid is washed with ether (115 mL, Note 7) and the filtrate is concentrated under reduced pressure to give an orange-brown oil (ca. 15 g). The collected solid is triturated with methylene chloride (2.0 L) and the insoluble inorganic salts are removed by filtration using a Büchner funnel. The orange-brown oil (ca. 15 g) is taken up in water (150 mL) and extracted with methylene chloride (6 x 270 mL). The combined methylene chloride extracts and methylene chloride triturate are dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 23-31 g (44-51%) of pure dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate as an orange-yellow powder: mp 171-172°C (Note 8).

D. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (20 g, 0.1 mol) is slurried in 800 mL of methylene chloride (Note 9) in a 2-L, round-bottomed flask fitted with a magnetic stirring bar and the mixture is cooled with an ice/water bath. A stream of nitrous gases (Note 10) is bubbled into the reaction mixture with stirring for 15 min. The color of the reaction mixture changes from orange to bright red during the addition. Stirring is continued for 1.5 hr as the reaction mixture is allowed to warm to room temperature. The solvent and excess nitrous gases are removed under reduced pressure to afford dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (19.7 g, 99%) as a bright red, crystalline solid: mp 173-175°C (Note 11).

E. Dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate. A 50-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1.0 g, 0.005 mol) and 1,4-dioxane (20 mL, Note 12). 1-Phenyl-1-(trimethylsiloxy)ethylene (1.07 g, 0.0056 mol, 1.14 mL, Note 13) is added and the reaction mixture is stirred under nitrogen at room temperature for 8 hr. The solvent is removed under reduced pressure to give a viscous oil that is triturated with anhydrous ether (2-3 mL). The solid product is collected by vacuum filtration and recrystallized from ethyl acetate/hexane to give 1.23-1.30 g (90-96%) of dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate as a light yellow solid, mp 95.5-96°C (Note 14).

F. Dimethyl 3-phenylpyrrole-2,5-dicarboxylate. A 250-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate (1.36 g, 0.005 mol) and glacial acetic acid (55 mL, Note 15). Zinc dust (3.25 g, 0.05 mol, Note 16) is added and the reaction mixture is stirred at room temperature for 6 hr. A second portion of zinc dust (3.25 g, 0.05 mol) is added and the reaction mixture is stirred for an additional 18 hr. The zinc dust is removed by filtration through a pad of Celite and the residue is washed with ether (100 mL). The filtrate and washes are combined, made basic (pH 10) with the addition of saturated sodium bicarbonate, and extracted with ether (2 x 100 mL). The combined ether extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the product is effected by flash chromatography on a 4.5 x 9-cm column of silica gel (Aldrich 951, CH₂Cl₂ eluant), collecting 20-mL fractions. The fractions are analyzed by thin-layer chromatography (Kieselgel 60, CH₂Cl₂ eluant) and those containing product are combined and concentrated in vacuo to give 0.676 g (52%) of dimethyl 3-phenylpyrrole-2,5-dicarboxylate as a white solid: mp 122-123°C (ethyl acetate-hexane, Note 17).

2. Notes

1. The submitters employed, without purification, ethyl diazoacetate obtained from Aldrich Chemical Company, Inc.

2. A time lag (10-15 min) is observed before the exothermic reaction begins. Addition of ethyl diazoacetate is then maintained at such a rate that the reaction temperature does not rise above 80°C. The checkers had to heat the mixture to 60°C.

3. Drying of the free acid should be rapid with a large surface area since traces of hydrochloric acid promote hydrolysis of the product to hydrazine salts. Slight warming ($\leq 60^{\circ}\text{C}$) during drying accelerates the drying process. The IR spectrum is as follows: IR (KBr) ν_{max} cm^{-1} : 3700-3100, 3320, 3000-1850, 1710, 1630. The checkers found that this step does not work as well on a smaller scale (0.14 mol).

4. Methanol is distilled from magnesium turnings immediately before use.

5. The submitters employed, without purification, thionyl chloride obtained from Fisher Scientific Company. The procedure should be performed in a well-ventilated hood since thionyl chloride is a lachrymator. The yield of dimethyl ester was found to be lower in instances when the thionyl chloride-methanol solution was not allowed to stir (30 min, -30°C) prior to the addition of dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid.

6. The temperature is maintained at -30°C during the additions.

7. The submitters employed ether distilled from sodium benzophenone ketyl.

8. The spectral properties of the product are as follows: ^1H NMR (CDCl_3) δ : 3.92 (s, 6 H, CO_2CH_3), 7.42 (br s, 2 H, NH); IR (KBr) ν_{max} cm^{-1} : 3160, 3050, 1740, 1720.

9. The submitters employed methylene chloride from Fisher Scientific Company, which was distilled before use.

10. Nitrous gases are generated in a separate vessel by the disproportionation of nitrous acid (HONO): 200 mL of 6 N NaNO_2 (1.2 mol) is added dropwise to 125 mL of concentrated hydrochloric acid (1.5 mol) in a 500-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet, a 500-mL addition funnel, and an outlet tube leading to the reaction flask. The brown gases evolved are bubbled directly into the reaction mixture through a 5-mm (inside diameter) glass tube (smaller inlet tubes occasionally became plugged) using a nitrogen stream. *Caution: all operations involving nitrous gases should be conducted in a well-ventilated hood because of the toxicity of these gases.*

11. The checkers observed some starting material in the product which depressed the mp. It could be removed by crystallization from ethyl acetate to give pure **3**, mp 176-177°C, but with significant loss of product. The spectral properties of the product are as follows: ^1H NMR (CDCl_3) δ : 4.22 (s, 6 H, CO_2CH_3); IR (KBr) ν_{max} cm^{-1} : 2970, 1752, 1445, 1385, 1219, 1175, 1082, 960, 912; UV (dioxane) λ_{max} (log ϵ) 520 nm (2.754).

12. The submitters employed 1,4-dioxane obtained from Fisher Scientific Company and distilled before use.

13. The submitters employed, without purification, 1-phenyl-1-(trimethylsiloxy)ethylene obtained from Aldrich Chemical Company, Inc.

14. The elemental analysis and the spectral analysis of the product are as follows: Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 62.01; H, 4.50; N, 10.19; ^1H NMR (CDCl_3) δ : 3.89 (s, 3 H, CO_2CH_3), 4.12 (s, 3 H, CO_2CH_3), 7.40-7.60 (m, 5 H, Ph), 8.27 (s, 1 H, C5-H); IR (KBr) ν_{max} cm^{-1} : 2955, 1742, 1584, 1447, 1399, 1287, 1244, 1142, 700; EI-MS (70 eV): m/e (relative intensity) 272 (M^+ , 9), 242 (7), 241 (6), 214 (34), 182 (10), 155 (base), lit^{2b} mp 94-95.5°C.

15. The submitters employed, without purification, glacial acetic acid obtained from Fisher Scientific Company.

16. Zinc dust obtained from Fisher Scientific Company was activated prior to use following an established procedure.³

17. The elemental analysis and the spectral analysis of the product are as follows: Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.10; H, 4.99; N, 5.48; 1H NMR ($CDCl_3$) δ : 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.94 (d, 1 H, $J = 3$, C4-H), 7.30-7.60 (m, 5 H, Ph), 9.80 (br s, 1 H, NH); IR (KBr) ν_{max} cm^{-1} : 3314, 2958, 1726, 1564, 1464, 1436, 1270, 1096, 1008, 940, 846, 762, 696. The additional formation of methyl 3-phenyl-5-carboxamidopyrrole-2-carboxylate in 32% yield is observed. The spectral properties of the product are as follows: 1H NMR ($CDCl_3$) δ : 1.75 (br s, 2 H), 3.92 (s, 3 H), 7.14 (s, 1 H), 7.40-7.60 (m, 5 H); IR (KBr) ν_{max} cm^{-1} : 3442, 3346, 2950, 1708, 1642, 1580, 1528, 1476, 1366, 1280, 1132, 1022, 936, 808, 728, 618; CI-MS (70 eV): m/e (relative intensity) 245 ($M^+ + H$, base).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

The procedure describes the preparation and use of a reactive, electron-deficient heterocyclic azadiene suitable for Diels-Alder reactions with electron-rich, unactivated, and electron-deficient dienophiles.⁴ Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, because of its electron-deficient character, is ideally suited for use in inverse electron demand ($LUMO_{diene}$ -controlled)⁵ Diels-Alder reactions. Table I and Table II detail representative examples of the reaction of dimethyl 1,2,4,5-tetrazine-3,6-

dicarboxylate with electron-rich carbon dienophiles^{6d} and heterodienophiles,^{4a,b,c} respectively. Complete surveys of the reported Diels-Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate have been compiled.⁴ Reductive ring contraction of the substituted dimethyl 1,2-diazine-3,6-dicarboxylate [4 + 2] cycloadducts effected by zinc in acetic acid provides the corresponding substituted dimethyl pyrrole-2,5-dicarboxylates.^{6d,7} Table III details representative examples of this general reductive ring contraction reaction.^{7,8}

This approach to 1,2-diazine and pyrrole introduction based on the inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate complements the [4 + 2] cycloaddition reactions of a range of electron-deficient heterocyclic azadienes which permits the divergent preparation of a range of heterocyclic agents employing a common dienophile precursor, Scheme I.

1. Department of Chemistry, Purdue University, West Lafayette, IN 47907.
2. The procedure described for the preparation of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate is an adaptation of two detailed preparations: (a) Spencer, G. H., Jr.; Cross, P. C.; Wiberg, K. B. *J. Chem. Phys.* **1961**, *35*, 1939; (b) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, *98*, 1435. (c) The oxidation of dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate to dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate using nitrous gases is a modification of a previously described procedure,^{2b} see: Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer, J. *J. Org. Chem.* **1985**, *50*, 5377. For the original description of the base-promoted dimerization of ethyl diazoacetate, see: Curtius, Th.; Darapsky, A.; Müller, E. *Chem. Ber.* **1906**, *39*, 3410; **1907**, *40*, 84; **1908**, *41*, 3161; Curtius, Th.; Lang, J. *J. Prakt. Chem.* **1888**, *38*, 531; Hantzsch, A.; Lehmann, M. *Chem. Ber.* **1900**, *33*, 3668; Hantzsch, A.; Silberrad, O. *Chem. Ber.* **1900**, *33*, 58.

3. Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p. 1276.
4. (a) Neunhoeffer, H.; Wiley, P. F. "The Chemistry of Heterocyclic Compounds" In "Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines"; Wiley: New York; 1978, Vol. 33; (b) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869; (c) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781; (d) Boger, D. L.; Weinreb, S. M. "Hetero Diels-Alder Methodology in Organic Synthesis"; Academic Press, FL; 1987; (e) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
5. Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.
6. (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621; (b) Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1983**, *24*, 4511; (c) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745; (d) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405
7. Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481.
8. For additional examples, see: Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405.

Scheme 1

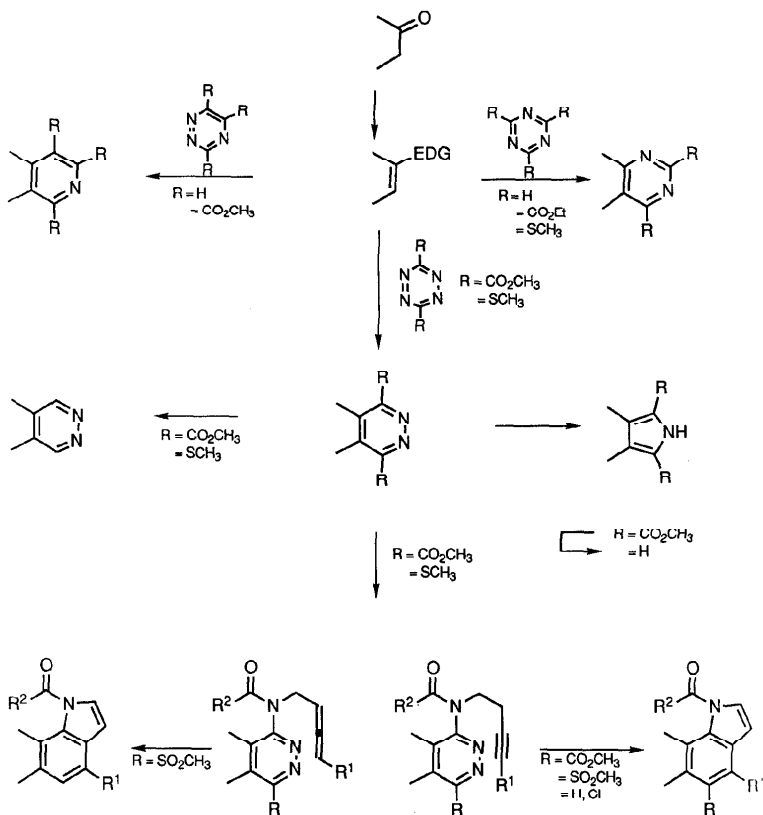





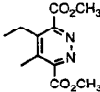

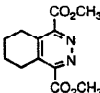



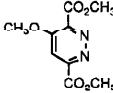

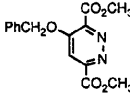

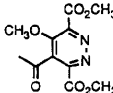
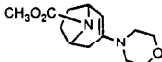
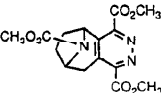


TABLE I

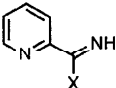
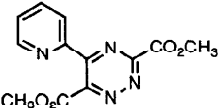
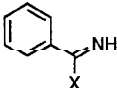
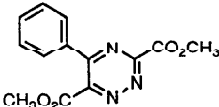
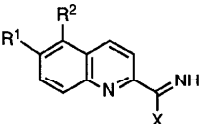
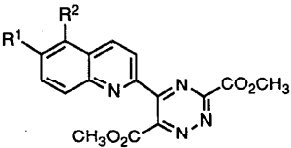
Diels-Alder Reactions of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate: 1,2-Diazine Introduction^{6d}

Entry	Dienophile	Conditions ^a Equiv. Temp °C (time hr)	1,2-Diazine	% Yield
1		1.5, 25(12)		1 87
2		2-6, 25(12)		1 trace
3	X = morpholine = pyrrolidine			2 70 trace
4		2, 25(48) 2, 25(48)		
5		1.5, 25(12)		3 85
6	X = OSi(CH ₃) ₃ = morpholine = pyrrolidine			4 92 87 trace
7		1, 25(5) 1.2, 25(1.5)		
8		1.5, 25(12)		
9		1.5, 25(0.5)		5 65
10	R = Si(Me) ₂ -t-Bu			6 33
11		PhCH ₂ O≡C-H		
12		2.5, 101(3)		7 71
13		1.25(5)		8 69

(a) All Diels-Alder reactions were carried out in dioxane.


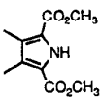
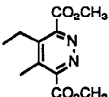
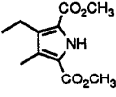
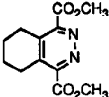
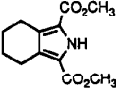
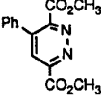
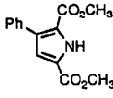
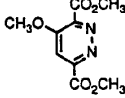
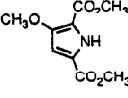
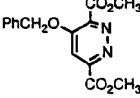
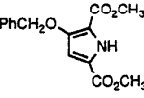
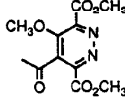
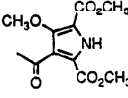
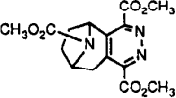
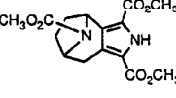
TABLE II

Diels-Alder Reaction of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate with C=N Heterodienophiles^{6a-c}

Dienophile	Conditions Temp °C (time hr) ^a	Product	% Yield
			
X = SCH ₃	80(20)		68
= OEt	80(8-12)		37
= NH ₂	25(5)		-
= NEt ₂	25-50(25)		-
			
X = SCH ₃	80(24)		65
= OEt	60(10)		27
= NH ₂	25(5)		-
			
R ¹ = R ² = H			70
X = SCH ₃	80(4)		33
= OEt	80(20)		
R ¹ = OCH ₃ R ² = H			78
X = SCH ₃	80(4)		
R ¹ = OCH ₃ R ² = NO ₂			82
X = SCH ₃	80(20-24)		

(a) All Diels-Alder reactions were carried out in dioxane.

TABLE III
Reductive Ring Contraction of Substituted Dimethyl 1,2-Diazine-3,6-dicarboxylates: Pyrrole Introduction^{6d}

Entry	1,2-Diazine	Conditions ^a Temp °C (time hr)	Pyrrole	%Yield
1		25(24)		63
2		25(24)		70
3		25(22)		52
4		25(9)		65
5		25(24)		67
6		25(24)		62
7		25(24)		56
8		25(36)		48

(a) All zinc (9-20 molar equiv) reductions were carried out in acetic acid (0.09 M in substrate).

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate: s-Tetrazine-3,6-dicarboxylic acid, dimethyl ester (8); 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, dimethyl ester (9); (2166-14-5)

Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate: 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, 1,2-dihydro-, disodium salt (11); (96898-32-7)

Ethyl diazoacetate: Acetic acid, diazo-, ethyl ester (8,9); (623-73-4)

Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate: 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, 1,2-dihydro- (9); (3787-09-5)

Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate: 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, 1,2-dihydro-, dimethyl ester (9); (3787-10-8)

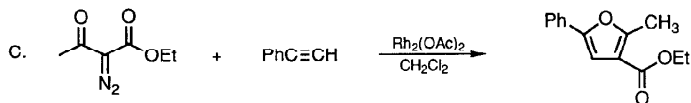
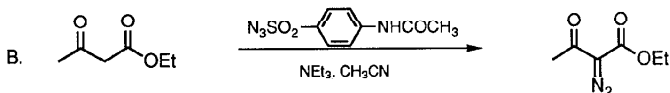
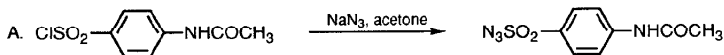
Thionyl chloride (8,9); (7719-09-7)

Dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate: 3,6-Pyridazinedicarboxylic acid, 4-phenyl-, dimethyl ester (9); (2166-27-0)

1-Phenyl-1-(trimethylsiloxy)ethylene: Silane, trimethyl[(1-phenylethenyl)oxy]- (9); (13735-81-4)

Dimethyl 3-phenylpyrrole-2,5-dicarboxylate: 1H-Pyrrole-2,5-dicarboxylic acid, 3-phenyl-, dimethyl ester (11); (92144-12-2)

**SYNTHESIS OF FURANS VIA RHODIUM(II) ACETATE-CATALYZED
REACTION OF ACETYLENES WITH α -DIAZOCARBONYLS:
ETHYL 2-METHYL-5-PHENYL-3-FURANCARBOXYLATE
(3-Furancarboxylic acid, 2-methyl-5-phenyl-, ethyl ester)**



Submitted by Huw M. L. Davies,¹ William R. Cantrell, Jr.,¹ Karen R. Homines,¹ and Jonathan S. Baum.²

Checked by Frank Stappenbeck and James D. White.

1. Procedure

Caution! These reactions, which involve toxic reagents, should be carried out in an efficient hood. Although p-acetamidobenzenesulfonyl azide exhibited no impact sensitivity,³ proper caution should be exercised with all azide compounds.

A. *p*-Acetamidobenzenesulfonyl azide.³ A 2-L Erlenmeyer flask equipped with a magnetic stirrer is charged with 117.0 g (0.50 mol) of *p*-acetamidobenzenesulfonyl

chloride (Note 1) and 1 L of acetone. A solution of 39.0 g (0.60 mol) of sodium azide in 300 mL of water is added with stirring and the resulting mixture is left to stir for 12 hr. Three 2-L beakers equipped with magnetic stirrers are charged with 1.5 L each of water. The reaction mixture is divided into three portions and poured into the beakers with stirring. After the mixture is stirred for 1 hr, the white precipitate is filtered (Note 2) and dried in a desiccator over sodium hydroxide for 24 hr. Recrystallization of this material in four portions from toluene (1.5 L each portion), while the temperature is maintained below 80°C (Note 3), affords 88.9 g (74%) of p-acetamidobenzenesulfonyl azide as white crystals, mp 113°-115°C (Note 4).

*B. Ethyl diazoacetoacetate.*³ A 2-L, round-bottomed flask equipped with a magnetic stirrer is charged with 26.0 g (0.20 mol) of ethyl acetoacetate, 49.0 g, (0.20 mol) of p-acetamidobenzenesulfonyl azide and 1.5 L of acetonitrile. The reaction vessel is cooled in an ice bath, and 60.6 g (0.60 mol) of triethylamine is added to the stirring mixture in one portion. The reaction mixture is warmed to room temperature and stirred for 12 hr. The solvent is removed under reduced pressure, and the residue is triturated with 500 mL of a 1:1 mixture of ether/petroleum ether. The mixture is filtered to remove the sulfonamide by-product, and the filtrate and wash are concentrated under reduced pressure. The crude product is purified by chromatography on silica gel (130 g, Note 5) with ether/petroleum ether (1:4) as eluant to yield 28.5 g (91%) of ethyl diazoacetoacetate as a yellow oil (Note 6).

*C. Ethyl 2-methyl-5-phenyl-3-furancarboxylate.*⁴ A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel, and a reflux condenser is flushed with argon (Note 7). The reaction vessel is charged with 44.35 g of phenylacetylene (0.44 mol, Note 8), 0.36 g of rhodium(II) acetate dimer (0.00067 mol), and 100 mL of dichloromethane and the mixture is heated to reflux under an argon atmosphere. The addition funnel is charged with 13.57 g of ethyl diazoacetoacetate (0.087 mol) and 200 mL of dichloromethane, and this solution is

added dropwise over 1.5 hr to the reaction mixture. After the reaction mixture is heated under reflux for an additional 12 hr, it is cooled and the solvent is removed under reduced pressure. The crude product is purified by chromatography on silica gel (110 g) with ether/petroleum ether (1:19) as eluant, followed by vacuum distillation (10-cm Vigreux column, 130°C, 0.1 mm) to yield 9.95 g (50%) of the furan as a pale yellow liquid (Note 9).

2. Notes

1. The following chemicals were obtained from the Aldrich Chemical Company, Inc., and were used without further purification: p-acetamidobenzenesulfonyl chloride, 97%; acetone, 99.9+%, HPLC grade; sodium azide, 99%; ethyl acetoacetate, 99%; triethylamine, 99%; rhodium(II) acetate dimer; phenylacetylene, 98%. The following solvents were obtained from Fisher Scientific and were used without further purification: toluene, certified A. C. S.; ethyl ether (Solvent grade, Concentrated); petroleum ether, certified A. C. S. Dichloromethane was distilled from calcium hydride.

2. The filtrate contains excess sodium azide which should be destroyed prior to disposal.

3. The azide partially decomposes at temperatures exceeding 80°C, and the resulting crystals appear slightly brown.

4. Data for p-acetamidobenzenesulfonyl azide are as follows: $R_f = 0.49$ (ether/petroleum ether (1:4)); $^1\text{H NMR}$ (200 MHz, CDCl_3) δ : 2.23 (s, 3 H), 7.75-7.89 (m, 4 H), 8.02 (s, 1 H); IR (nujol) cm^{-1} : 3250, 2110, 1665, 1580. Anal. Calcd for $\text{C}_8\text{H}_8\text{N}_4\text{O}_3\text{S}$: C, 40.00; H, 3.36; N, 23.32; S, 13.35. Found: C, 40.10; H, 3.40; N, 23.26; S, 13.40.

5. Silica gel 60 230-400 mesh ASTM was used. Whatman 250-mm layer, UV254, silica gel TLC plates with polyester backing were used to analyze the fractions.

6. Spectral data for ethyl diazoacetoacetate are as follows: ^1H NMR (200 MHz, CDCl_3) δ : 1.29 (t, 3 H, $J = 7.1$), 2.43 (s, 3 H), 4.26 (q, 2 H, $J = 7.1$); IR (neat) cm^{-1} : 2970, 2130, 1700, 1650.

7. The glassware in this reaction is dried with a heat gun and placed in a drying oven for 1 hr prior to use.

8. A smaller amount of phenylacetylene results in inefficient capture of the carbenoid intermediate, leading to lower yields.

9. Data for ethyl 2-methyl-5-phenyl-3-furancarboxylate are as follows: $R_f = 0.51$ (ether/petroleum ether (1:9)); ^1H NMR (200 MHz, CDCl_3) δ : 1.35 (t, 3 H, $J = 7.1$), 2.63 (s, 3 H), 4.30 (q, 2 H, $J = 7.1$), 6.87 (s, 1 H), 7.24-7.40 (m, 3 H), 7.60-7.65 (m, 2 H); IR (neat) cm^{-1} : 3080, 3000, 1725, 1610, 1590, 1565. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 73.03; H, 6.13. Found: C, 73.17; H, 6.09.

Waste Disposal Information

Excess sodium azide in the filtrate was destroyed by treatment with ammonium cerium(IV) nitrate solution according to the procedure described by Lunn, G.; Sansone, E. B., In "Destruction of Hazardous Chemicals in the Laboratory"; Wiley: New York, 1990; p. 44.

3. Discussion

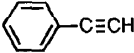
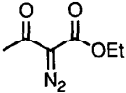
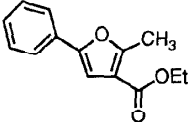
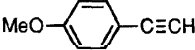
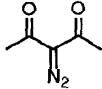
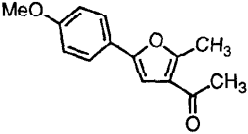
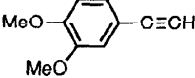
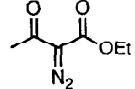
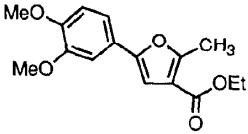
The procedure described here provides a direct synthesis of highly substituted furans (see Table). Reaction of keto carbenoids with acetylenes is normally an efficient method to prepare cyclopropenes.⁵ In numerous systems, however, the formation of furans was observed as a competing side reaction.⁶ Furan formation is particularly favored when the carbenoid is a pyruvate⁷ or contains two electron-withdrawing groups,^{4,8} and when electron-donating groups are present on the acetylene.^{4,8}

The diazo transfer reaction with sulfonyl azides has been used extensively for the preparation of diazo compounds.⁹ Toluenesulfonyl azide is the standard reagent used,¹⁰ but because of safety problems resulting from its potentially explosive nature, and because of the difficulty of product separation, several alternative reagents have been developed recently. n-Dodecylbenzenesulfonyl azide¹¹ has been reported to be very effective for the preparation of crystalline diazo compounds, while p-naphthalenesulfonyl azide¹¹ has been used for fairly non-polar compounds. Other useful reagents are methanesulfonyl azide¹² and p-carboxybenzenesulfonyl azide.¹³ p-Acetamidobenzenesulfonyl azide³ offers the advantages of low cost, safety, and ease of removal of the sulfonamide by-product through a simple trituration.

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2. Agricultural Chemical Group, FMC Corporation, P. O. Box 8, Princeton, NJ 08543.
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TABLE
RHODIUM(II) ACETATE-CATALYZED REACTION OF ACETYLENES
WITH DIAZO CARBONYL COMPOUNDS⁴

Acetylene	Diazo	Furan	Yield %
			50
			52
			69

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Rhodium(II) acetate dimer: Acetic acid, rhodium(2+) salt (8,9); (5503-41-3)

Ethyl 2-methyl-5-phenyl-3-furancarboxylate: 3-Furoic acid, 2-methyl-5-phenyl-, ethyl ester (8); 3-Furancarboxylic acid, 2-methyl-5-phenyl-, ethyl ester (9); (29113-64-2)

p-Acetamidobenzenesulfonyl azide: Sulfanilyl azide, N-acetyl- (8);

Benzenesulfonyl azide, 4-(acetylamino)- (9); (2158-14-7)

p-Acetamidobenzenesulfonyl chloride: Sulfanilyl chloride, N-acetyl- (8);

Benzenesulfonyl chloride, 4-(acetylamino)- (9); (121-60-8)

Sodium azide (8,9); (26628-22-8)

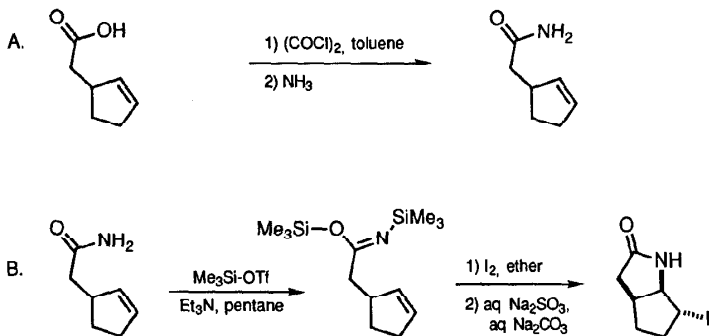
Ethyl diazoacetoacetate: Acetoacetic acid, 2-diazo-, ethyl ester (8); Butanoic acid, 2-diazo-3-oxo-, ethyl ester (9); (2009-97-4)

Ethyl acetoacetate: Acetoacetic acid, ethyl ester (8); Butanoic acid, 3-oxo-, ethyl ester (9); (141-97-9)

IODOLACTAMIZATION:

8-exo-iodo-2-azabicyclo[3.3.0]octan-3-one

(Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3 α ,6 α ,6 α)-)



Submitted by Spencer Knapp and Frank S. Gibson.¹

Checked by Chris Melville and James D. White.

1. Procedure

Caution! The following operations produce lachrymatory and corrosive vapors and must be carried out in a well-ventilated fume hood.

A. 2-Cyclopentene-1-acetamide. A dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, serum stopper, 25-mL pressure equalizing addition funnel, and an argon atmosphere with provision for venting gaseous reaction products (Note 1). The vessel is charged with 20 g (152 mmol) of 2-cyclopentene-1-acetic acid (Note 2) and 25 mL of dry toluene (Note 3). Oxalyl chloride (17.3 mL, 1.3 equiv) is added slowly over a 30-min period by means of the addition

funnel, taking care to release any pressure buildup. (*Caution: gaseous hydrogen chloride evolution!*). The dark reaction mixture is stirred for an additional 20 min while the second reaction vessel is assembled, then concentrated to about 2/3 volume at the vacuum pump (Note 4).

A 250-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, serum stopper, dry ice condenser, and argon atmosphere is cooled by means of a dry ice/acetone bath and charged with approximately 150 mL of dry liquid ammonia. The 2-(2-cyclopentenyl)acetyl chloride reaction mixture is added carefully but steadily (Note 5) to the cold and rapidly stirred ammonia by syringe. (*Caution: vigorous exothermic reaction!*). Residual acid chloride is transferred by rinsing the first vessel with 5 mL of toluene. After the addition the mixture is stirred for an additional 5 min, then 60 mL of dichloromethane is added. The cold bath is removed and the excess ammonia is allowed to escape into the fume hood by stirring the open vessel overnight.

The crude reaction mixture is filtered and the filtrate is reserved. The solids are triturated by stirring vigorously with 100 mL of methanol for 20 min with gentle warming to about 40°C. The solids are filtered and triturated again in the same way. The three organic filtrates are combined and concentrated to near dryness. The resulting semi-solid is redissolved in 100 mL of dichloromethane, filtered to remove residual ammonium chloride, and concentrated to a light brown solid, 18.9 g. The crude product is dissolved in 60 mL of boiling tetrahydrofuran and allowed to crystallize in a -6°C freezer overnight. The amide is collected by filtration, washed with 5 mL of cold ether, and dried under reduced pressure, giving 15.77 g of white flakes, mp 128-129°C. The filtrate is concentrated to about 8 mL, brought to the cloud point by the addition of a few drops of hexane, and cooled in the freezer. Filtration as before gives a second crop of white flakes, 1.46 g, mp 128-129°C (total yield 17.23 g, 90.6%) (Note 6).

B. 8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one. A dry, 500-mL, three-necked, round-bottomed flask equipped with magnetic stirring bar, serum stopper, 50-mL pressure-equalizing addition funnel, cold water bath, and argon atmosphere is charged with 12.5 g (100 mmol) of 2-cyclopentene-1-acetamide, 29.2 mL (210 mmol) of triethylamine (Note 7), and 80 mL of dry pentane (Note 8). By means of the addition funnel, 41 mL (210 mmol) of trimethylsilyl trifluoromethanesulfonate (Note 9) is slowly added to the cooled and rapidly stirred amide suspension over a 50-min period. After the addition is complete, the reaction mixture is stirred for an additional 20 min at room temperature, then the stirring is stopped, and the two layers are allowed to separate.

A second, dry, 500-mL, three-necked, round-bottomed flask is equipped with magnetic stirring bar, serum stopper, vacuum pump connection, and argon atmosphere. The (top) pentane layer from the first flask, which contains the bis(trimethylsilyl)imidate, is carefully transferred to the second flask by cannula, maintaining the argon atmosphere, and leaving the oily triethylammonium trifluoromethanesulfonate layer behind. This remaining salt is triturated with 30 mL of a dry 2:1 pentane/ether mixture by stirring for 15 min, allowing the layers to separate, then transferring the extract to the second flask as before. The trituration is repeated with a 30-mL portion of anhydrous ether, and the combined extracts in the second flask are concentrated with stirring to about 1/3 volume using the vacuum pump (Note 10).

A third, dry, 500-mL, three-necked, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, serum stopper, cold water bath, and argon atmosphere is charged with 53.3 g (210 mmol) of molecular iodine and 140 mL of anhydrous ether. The mixture is allowed to stir for 10 min to dissolve most of the iodine. The concentrated organic extract in the second flask is now added to the iodine solution with stirring and cooling over 15 min. The reaction mixture warms slightly during the addition, but should not reach reflux. An additional 10 mL of

anhydrous ether is used to complete the transfer of the bis(trimethylsilyl)imidate. Near the end of the addition, the oily black layer (which contains the cyclized iminium salt) solidifies, leaving a clear light brown ether supernatant. The serum stopper is carefully removed and the solid residue gently broken up using a spatula. The stopper is replaced and the reaction mixture is allowed to stand for an additional 45 min with occasional swirling by hand. The reaction is quenched by removing the addition funnel and stopper and slowly adding 20 mL of saturated aqueous sodium carbonate. (*Caution: vigorous gas evolution!*). At this point stirring can be resumed. A 20-mL portion of saturated aqueous sodium sulfite is added slowly (*more gas evolution*), and the process is repeated until 100 mL each of saturated aqueous sodium carbonate and sulfite have been added. The reaction mixture is filtered, the crude solid iodolactam is reserved, and the organic layer is separated and reserved. The aqueous layer is saturated with sodium chloride and extracted with four, 100-mL portions of dichloromethane. The five organic extracts are combined, dried over anhydrous sodium sulfate, and concentrated to a light brown solid. This residue is dissolved in 20 mL of tetrahydrofuran and hexane is added to the cloud point. Cooling in the freezer gives colorless needles, which are collected and dried under reduced pressure to afford 1.60 g of iodolactam, mp 138-139°C.

The reserved solid from filtration is dried under reduced pressure, dissolved in 65 mL of hot tetrahydrofuran and filtered. The solution is allowed to cool, first at room temperature, then in the freezer. The product (16.77 g, mp 138-139°C) is collected as before. The mother liquor is concentrated to about 10 mL, brought to the cloud point by the addition of hexane, and cooled in the freezer, resulting in an additional crop of 1.70 g, mp 138-139°C. The total amount of iodolactam is 19.80 g, representing a 79% yield from the amide (Note 11).

2. Notes

1. All reaction glassware was oven dried at 120°C and assembled hot. The submitters used three evacuate/fill cycles from an argon-filled balloon fitted on a three-way stopcock to provide the inert atmosphere.

2. 2-Cyclopentene-1-acetic acid (96%) was purchased from Aldrich Chemical Company, Inc., and used as received.

3. Toluene was dried by distillation from -40 mesh calcium hydride. Unless otherwise specified, reagents in this procedure were obtained commercially and used as received.

4. In series with the usual (500 mL) dry ice/acetone trap, a trap filled with solid sodium hydroxide was used to protect the pump from acidic vapors.

5. *Continuous addition of the carboxylic acid chloride solution is required to prevent clogging the syringe needle.*

6. The spectral properties are as follows: FT-IR (KBr) cm^{-1} : 3360, 3355, 1663, 1634; ^1H NMR (CDCl_3 , 400 MHz) δ : 1.42-1.49 (m, 1 H), 2.07-2.35 (m, 5 H), 3.06-3.09 (m, 1 H), 5.66 (br s, 1 H), 5.75 (app dd, 1 H, $J = 2, 5$), 5.76 (app dd, 1 H, $J = 2.5, 4.5$), 5.94 (br s, 1 H); ^{13}C NMR δ : 29.6, 31.8, 42.0, 42.3, 131.7, 133.7, 175.0.

7. Triethylamine was dried by distillation from -40 mesh calcium hydride.

8. Pentane was dried by distillation from -40 mesh calcium hydride.

9. Trimethylsilyl trifluoromethanesulfonate (99%) was purchased from Aldrich Chemical Company, Inc., and used as received.

10. Any adventitious water introduced during these operations results in a decreased yield of iodo lactam and the formation of iodo lactone as an undesired side product.

11. The spectral properties are as follows: FT-IR (KBr) cm^{-1} : 3189, 3078, 3034, 1680; ^1H NMR (CDCl_3 , 400 MHz) δ : 1.55-1.60 (m, 1 H), 1.99-2.06 (m, 1 H), 2.10-2.20 (m, 2 H), 2.33-2.45 (m, 1 H), 2.70 (dd, 1 H, $J = 18, 10$), 3.05-3.13 (m, 1 H), 4.16 (br s, 1 H), 4.40 (d, 1 H, $J = 7.2$), 5.75-5.85 (br s, 1 H); ^{13}C NMR δ : 32.3, 32.9, 35.0, 35.5, 38.2, 69.8, 178.6.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion


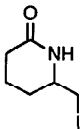

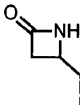

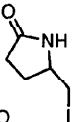
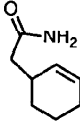
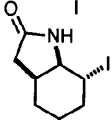
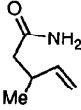
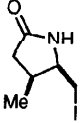
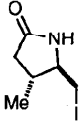
This "iodolactamization" procedure has been optimized for the present example. Related reaction conditions have been used to generate a series of iodo lactams from the corresponding unsaturated amides (Table).² For these (smaller scale) examples, the cyclization was carried out in tetrahydrofuran solution, and isolation was by column chromatography. The lactams in entries 3, 4, and 8 have also been recently prepared by the submitters in 81%, 82%, and 78% yields, respectively, using the procedure described here. Cyclization in ether solution rather than in tetrahydrofuran avoids the formation of iodobutanol,² which must then be separated from product.

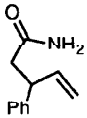
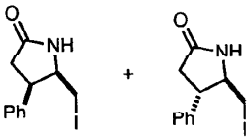
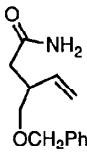
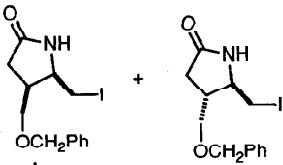
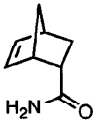
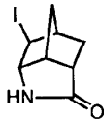
Iodo lactams are a useful, new class of difunctional compounds. Conversions of iodo lactams to N-acylaziridines,^{2,3} unsaturated lactams,^{2,4} azido lactams,^{2,3} amino lactams,^{2,3} hydroxy lactams,² annulated lactams,^{2,5} and other derivatives have been described. Halo lactams have also been prepared from aspartic acid⁵ and glutamic

acid,⁶ from N-substituted unsaturated amides⁷⁻⁹ and imidates,¹⁰⁻¹² and from unsaturated amides whose competing O-cyclization reaction is less favored.^{13,14}

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TABLE
PREPARATION OF IODO LACTAMS

Entry	Unsaturated Amide	Iodo Lactam(s)	% Yield (cis/trans)
1			35 ^a
2			35 ^b
3			86
4			88
5		 + 	84 (3:1)

Entry	Unsaturated Amide	Iodo Lactam(s)	% Yield (cis/trans)
6			88 (2:1)
7			86 (1:1)
8			80 ^c

^a10-20% of starting amide was also recovered. ^b54% of crotonamide was also isolated. ^cOverall yield after separate desilylation.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

8-exo-iodo-2-azabicyclo[3.3.0]octan-3-one: Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3 α ,6 α ,6 α)- (11); (100556-58-9)

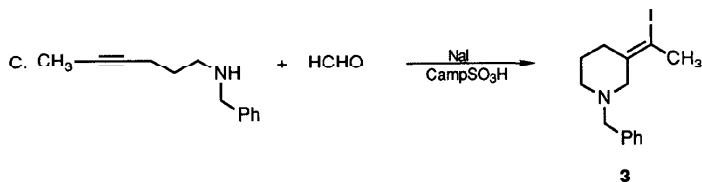
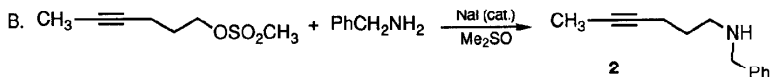
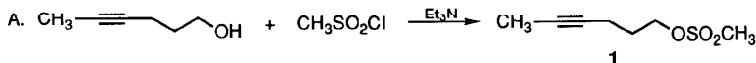
2-Cyclopentene-1-acetamide (10); (72845-09-1)

2-Cyclopentene-1-acetic acid (8,9); (13668-61-6)

Oxalyi chlorido (8); Ethanedioyl dichloride (9); (79-37-8)

Trimethylsilyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, trimethylsilyl ester (8,9); (27607-77-8)

(E)-1-BENZYL-3-(1-iodoethylidene)PIPERIDINE: NUCLEOPHILE-PROMOTED ALKYNE-IMINIUM ION CYCLIZATIONS



Submitted by H. Arnold, L. E. Overman, M. J. Sharp and M. C. Witschel.¹

Checked by Antje Grützmann, Thomas Hache, and Ekkehard Winterfeldt.

1. Procedure

A. 4-Hexyn-1-yl methanesulfonate (1). An oven-dried, 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is flushed with argon and 260 mL of dichloromethane is added (Note 1). The flask is sealed with a rubber septum inlet and cooled to ca. -10°C in an ice-salt bath. To this flask are added via syringe 11 mL (80 mmol) of triethylamine, 5.0 g (51 mmol) of 4-hexyn-1-ol (Note 2), and 4.3 mL (56 mmol) of methanesulfonyl chloride (Note 3). The resulting solution is

stirred for an additional 30 min and then quenched by adding 30 mL of ice-water. The organic layer is separated and washed successively with 1 M hydrochloric acid solution (30 mL), saturated aqueous sodium bicarbonate solution (30 mL), and brine (30 mL). The organic layer is dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give 8.3-9.0 g (93-100%) of crude 4-hexyn-1-yl methanesulfonate (**1**) which was used directly in the next step (Note 4).

B. N-Benzyl-4-hexyn-1-amine (2). An oven-dried, 100-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a rubber septum inlet is flushed with argon and charged with 200 mg of sodium iodide. The crude mesylate **1**, 40 mL of dimethyl sulfoxide (Note 5) and 10.9 g (102 mmol) of benzylamine are added via syringe. The resulting solution is heated in an oil bath at 47-53°C for 5 hr (Note 6) and then allowed to cool to room temperature. The reaction solution is poured into a separatory funnel containing 200 mL of aqueous 1% sodium hydroxide solution and the resulting mixture is extracted with ether (3 x 100 mL). The combined ether extracts are washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue (ca. 9 g) is purified by flash chromatography (ca. 300 g of silica gel using 1:1 hexane-ether containing 5% triethylamine as the eluent) (Note 7) to give 7.2-7.5 g (75-79% overall) of **2** as a colorless liquid (Note 8).

C. (E)-1-Benzyl-3-(1-iodoethylidene)piperidine (3). A 250-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a reflux condenser topped with a rubber septum inlet is flushed with argon and charged with 4.0 g (21 mmol) of alkynylamine **2**, 11 g (73 mmol) of sodium iodide (Note 9), 35 mL of 37% w/w formaldehyde solution, 5.4 g (22 mmol) of camphorsulfonic acid monohydrate (Note 10) and 80 mL of water. The resulting mixture is heated at reflux under an argon atmosphere for 15 min (Note 11) and then allowed to cool to room temperature. This solution is made basic by adding 5 M aqueous potassium hydroxide solution and then

poured into a separatory funnel where it is extracted with dichloromethane (3 x 50 mL) (Note 12). The combined organic layers are dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The resulting residue is purified by flash chromatography (ca. 150 g of silica gel, 1:1 hexane-ethyl ether containing 5% triethylamine as eluent) to give 5.4-6.2 g (79-90%) of **3** as a colorless oil (Notes 13 and 14).

2. Notes

1. Dichloromethane is distilled from calcium hydride (CaH_2) and added directly from the still to the reaction flask.

2. This alcohol is readily prepared in standard fashion from the tetrahydropyranyl ether of 4-pentyn-1-ol and iodomethane: A hexane solution of butyllithium (46 mL of a 2.2 M solution, 100 mmol) is added dropwise under an argon atmosphere to a dry ice-cooled solution of tetrahydro-2-(4-pentynyloxy)-2H-pyran (14.4 g, 84 mmol, prepared from commercially available 4-pentyn-1-ol²) in 100 mL of dry tetrahydrofuran. After 10 min, 7.0 mL (110 mmol) of iodomethane is added dropwise to the dry ice-cooled, stirring solution of the alkynyllithium intermediate. The reaction mixture is maintained at dry ice temperature for 1 hr, and, after warming to room temperature, the tetrahydrofuran is removed by mild rotary evaporation (or distillation at atmospheric pressure). The crude product is dissolved in 100 mL of ether and washed with brine (50 mL), and the aqueous phase is back-extracted with ether (25 mL). The combined organic phases are concentrated and the residue is dissolved in 200 mL of methanol. *p*-Toluenesulfonic acid (4 g) is added and the resulting solution is heated at reflux for 3 hr. The solvent is removed by distillation through an 8-10 cm Vigreux column, the residue is dissolved in 100 mL of ether and this solution is extracted with 25 mL of aqueous 10% sodium carbonate solution. After

the solution is dried over MgSO_4 , the solvent is removed by distillation and the residue is distilled through a 50-cm concentric tube column. The fraction boiling at 92-93°C (10 mm Hg) is collected to give 7.8 g (94%) of 4-hexyn-1-ol, which is >95% pure by GC analysis (30 m, Supelco SPB-5 capillary column).

3. Triethylamine, distilled from CaH_2 , and methanesulfonyl chloride, vacuum distilled at ca. 60°C (20 mm), are employed.

4. The spectrum is as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.78 (t, 3 H, $J = 2.5$), 1.91 (apparent pentaplet, 2 H, $J = 6.5$), 2.25-2.35 (m, 2 H), 3.03 (s, 3 H), 4.35 (t, 2 H, $J = 6.1$).

5. Dimethyl sulfoxide, distilled at 20 mm from CaH_2 , and benzylamine, freshly distilled at 20 mm, are employed.

6. The reaction is easily monitored by TLC (silica gel, 1:1 ether-ethyl acetate): mesylate $R_f = 0.9$, amine $R_f = 0.4$.

7. This material can also be purified by vacuum distillation; however, some decomposition results.

8. This material is 97% pure by capillary GC analysis (30 m, J & W DB-5 fused silica column). Spectral data are as follows: IR (film) cm^{-1} : 3330, 1453, 1120, 736; ^1H NMR (300 MHz, CDCl_3) δ : 1.69 (apparent pentaplet, 2 H, $J = 7$), 1.77 (t, 3 H, $J = 2.5$), 2.15-2.25 (m, 2 H), 2.73 (t, 2 H, $J = 7.0$), 3.80 (s, 2 H), 7.2-7.4 (m, 5 H); Mass spectrum (isobutane CI): 188 (MH), 172, 120, 91; high resolution mass spectrum (70 eV, EI) 187.1331 (187.1261 Calcd for $\text{C}_{13}\text{H}_{17}\text{N}$).

9. Fisher *Certified* sodium iodide is used as received.

10. Fisher *Certified* A.C.S. formaldehyde solution is used as received. Aldrich Chemical Company, Inc., camphorsulfonic acid monohydrate is recrystallized from ethyl acetate prior to use.

11. This conversion is easily monitored by TLC (silica gel, 1:1 hexane-ethyl acetate containing 5% triethylamine): 2. $R_f = 0.4$, 3. $R_f = 0.7$.

12. The free base of this iodoamine darkens slowly when exposed to room light. The isolation procedure should be conducted rapidly or the separatory funnel and rotary evaporator bulb should be wrapped in aluminum foil to exclude room light.

13. This material is at least 95% pure by capillary GC analysis (30 m, J & W DB-5 fused silica column); a small unknown impurity (ca. 2%) with characteristic ^1H NMR signals at δ 3.41, 4.77 and 4.92 is apparent in some chromatography fractions. Spectral data for **3** are as follows: IR (film) cm^{-1} : 1646, 1228, 1138, 1119, 1061, 739; ^1H NMR δ : 1.55-1.8 (m, 2 H), 2.40 (t, 2 H, $J = 6.3$), 2.45 (s, 3 H), 2.56 (t, 2 H, $J = 5.5$), 3.10 (s, 2 H), 3.57 (s, 2 H), 7.2-7.4 (m, 5 H); mass spectrum (isobutane CI): 328 (MH), 202, 200, 112, 110, 92. High resolution mass spectrum (70 eV, EI): 327.0465 (327.0484 calcd for $\text{C}_{14}\text{H}_{18}\text{NI}$).

14. The maleate salt is prepared in good yield and crystallizes as fine needles (ca. 1 g of salt/10 mL) from absolute ethanol: mp 143-144°C. This salt can be stored at room temperature in room light with no noticeable decomposition. Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{INO}_4$: C, 40.77; H, 5.00; N, 3.16. Found: C, 40.70; H, 5.00; N, 3.09.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

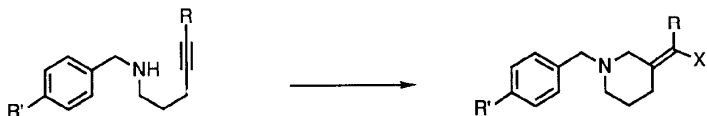
Simple alkynes do not undergo intramolecular reactions with weakly electrophilic iminium ions in the absence of strong external nucleophiles.³ For example, the formaldiminium ion derived from 4-hexynylamine, formaldehyde, and

camphorsulfonic acid does not cyclize when maintained in acetonitrile at 100°C for 1 hr.³ Iminium ion-alkyne cyclizations do take place in nucleophilic solvents such as H₂O⁴ or in non-nucleophilic solvents when a strong nucleophile is present.³

The present procedure illustrates the use of added iodide anion to promote the Mannich cyclization of an alkyne to afford 3-alkylidenepiperidines. As illustrated in Table I a variety of nonbasic nucleophiles with nucleophilic constants⁵ $\eta\text{-CH}_3\text{I} > 5.8$ are useful promoters of formaldiminium ion-alkyne cyclizations.³ Piperidines containing both endocyclic and exocyclic allylic unsaturation can be efficiently assembled in this way from readily available alkynol precursors (see Table I).³ To the limits of ¹H NMR detection at 500 MHz all nucleophile-promoted cyclizations that form 3-alkylidenepiperidines occur with complete anti-stereoselectivity.

The usefulness of nucleophile-promoted iminium ion-alkyne cyclizations derives from the ready availability of alkynylamines and the subsequent transformations of the cyclization products made possible because of their vinylic functionality (e.g., equations 1 and 2). Equation 2 illustrates use of this chemistry to elaborate an exocyclic tetrasubstituted double bond with complete stereocontrol. Net "reductive" iminium ion alkyne cyclizations can be accomplished by dehalogenation of vinyl halide cyclization products. The conversion illustrated in equation 3 is a key step in an efficient, practical synthesis of the cardiotoxic frog alkaloid pumiliotoxin A.⁶

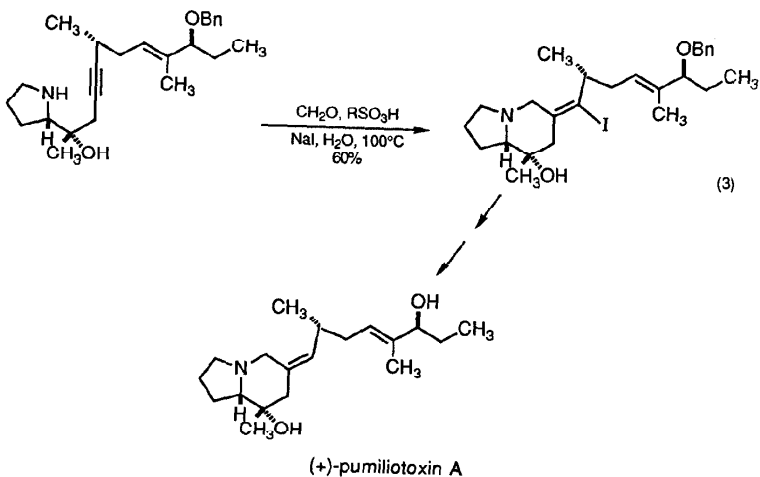
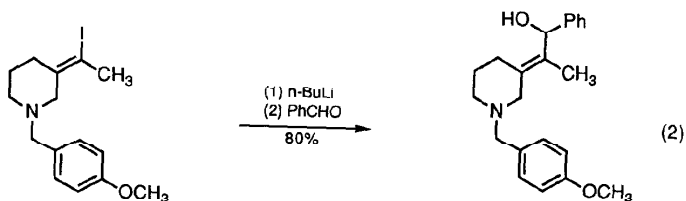
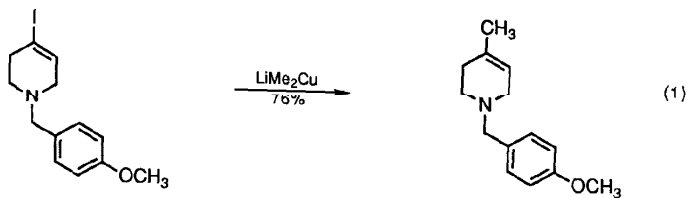
TABLE I. Nucleophile-Promoted Iminium Ion-Alkyne Cyclizations³



R'	R	X	Yield
OCH ₃	CH ₃	Br	89%
OCH ₃	CH ₃	I	80%
OCH ₃	n-Bu	Br	63% ⁷
OCH ₃	n-Bu	I	76% ⁷
H	CH ₃	I	81-90%
H	CH ₃	N ₃	72%
H	CH ₃	SCN	82%
OCH ₃	H	I	56%
OCH ₃	CH ₃	SPh	<15%



R	X	Yield
CH ₃	Br	75%
CH ₃	I	90%
CH ₃	N ₃	40%
Me ₃ Si	Br	44%
Me ₃ Si	I	60%
H	I	87%



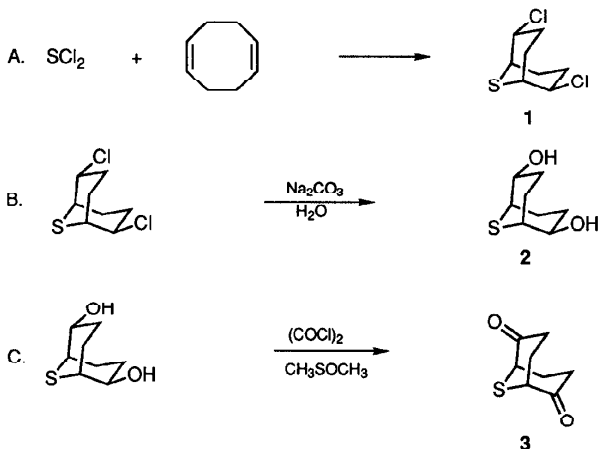
1. Department of Chemistry. University of California. Irvine. CA 92717.
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6. Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901.
7. Sharp, M. J. unpublished examples.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Hexyn-1-yl methanesulfonate: 4-Hexyn-1-ol, methanesulfonate (10); (68275-05-8)
 4-Hexyn-1-ol (8,9); (928-93-8)
 4-Pentyn-1-ol (8,9); (5390-04-5)
 Tetrahydro-2-(4-pentynyloxy)-2H-pyran: 2H-Pyran, tetrahydro-2-(4-pentynyloxy)-
 (10); (62992-46-5)
 Iodomethane: Methane, iodo- (8,9); (74-88-4)
 Methanesulfonyl chloride (8,9); (124-63-0)
 N-Benzyl-4-hexyn-1-amine: Benzenemethanamine, N-4-hexynyl- (12); (112069-91-7)
 Dimethyl sulfoxide: Methyl sulfoxide
 (8); Methane, sulfinyl bis- (9); (67-68-5)
 Benzylamine (8); Benzenemethanamine (9); (100-46-9)
 Sodium iodide (8,9); (7681-82-5)
 Formaldehyde (8,9); (50-00-0)
 Camphorsulfonic acid monohydrate: Bicyclo[2.2.1]heptane-1-methanesulfonic acid,
 7,7-dimethyl-2-oxo-, (\pm)- (9); (5872-08-2)

9-THIABICYCLO[3.3.1]NONANE-2,6-DIONE



Submitted by Roger Bishop.¹

Checked by Graham N. Maw and Robert K. Boeckman, Jr.

1. Procedure

A. *(1α,2α,5α,6α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (1). (Caution! Preparation A should be carried out in a well-ventilated hood).* A dry, 2-L, four-necked, round-bottomed flask is equipped with a sealed mechanical stirrer (Note 1), 1-L pressure-equalizing funnel fitted with a drying tube, low temperature thermometer, and a nitrogen inlet. The flask is charged with 125 mL (1.02 mol) of 1,5-cyclooctadiene (Note 2) and 1 L of reagent dichloromethane, cooled to -50 to -60°C using an external acetone-dry ice bath, and the solution placed under a slow stream of dry nitrogen. To

the vigorously stirred solution is added slowly over a period of 2 hr a solution of 65 mL (1.02 mol) of freshly purified sulfur dichloride (Note 3) in 500 mL of dichloromethane while maintaining the temperature at, or below, -50°C. The cloudy solution is allowed to warm to room temperature and filtered to remove a small amount of white solid. The filtrate is transferred to a 3-L separatory funnel, washed with brine (3 x 100 mL), and dried (Na₂SO₄). Solvent is removed from the filtrate under reduced pressure with a rotary evaporator to afford 201.4-210.8 g (94-98%) of (1 α ,2 α ,5 α ,6 α)-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (**1**) as a faintly yellow solid, mp 97.5-99°C (Note 4).

B. (endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (2). To a 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is added 21.12 g (0.10 mol) of the dichloride (**1**), 100 mL of acetone, and a solution of 34.33 g (0.12 mol) of sodium carbonate decahydrate (Note 5) in 200 mL of water. A condenser is attached to the flask. the contents are stirred gently and then heated to reflux. After 1 hr at reflux (bath temperature ca. 85°C) the clear solution is allowed to cool to room temperature and the stirrer bar is removed (Note 6). Solvent is removed under reduced pressure using a rotary evaporator until the aqueous slurry of white solid is reduced to roughly 25 mL and then the solid is removed by suction filtration at room temperature. The dried, crude diol is heated with 300 mL of methanol and the hot solution filtered directly into a 500-mL, round-bottomed flask, thereby removing small quantities of solid impurity (Note 7). A rotary evaporator is used to concentrate the solution to a volume of ca. 40 mL, and the resulting slurry is filtered to yield 15.2-16.2 g (87-93%) of (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (**2**) as a white solid (Notes 8, 9).

C. 9-Thiabicyclo[3.3.1]nonane-2,6-dione (3). (Caution! Oxalyl chloride and dimethyl sulfoxide are reported to react explosively at room temperature. Preparation C should be carried out in a well-ventilated hood since a co-product of the reaction is dimethyl sulfide). To a 1-L, three-necked flask equipped with a magnetic stirring bar, low temperature thermometer, dropping funnel protected from moisture by a drying

tube, and a second drying tube, is added 13.5 mL (0.16 mol) of oxalyl chloride and 350 mL of dichloromethane. The solution is stirred and cooled to -78°C using an external acetone-dry ice bath. A solution of 22.0 mL (0.31 mol) of dry dimethyl sulfoxide (Note 10) in 75 mL of dichloromethane is added over 10 min ensuring that the reaction temperature does not exceed -60°C . After a further 10 min a solution of 13.07 g (0.08 mol) of (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (**2**) in 30 mL of dry dimethyl sulfoxide is added rapidly from the dropping funnel to the stirred solution at -78°C (Note 11). Final traces of the solution are washed into the reaction using a further 10 mL of dry dimethyl sulfoxide. The reaction is stirred for 25 min at -78°C after addition of diol **2** is complete and then 105 mL of redistilled triethylamine is added dropwise. After a further 15 min at -78°C the cooling bath is removed and the reaction is allowed to warm to room temperature whereupon 300 mL of water is added. The material is transferred to a 2-L separatory funnel, the dichloromethane layer is separated, and the aqueous layer is extracted with two 100-mL portions of dichloromethane. The combined dichloromethane extracts are washed successively with 1 L of 1% hydrochloric acid, 300 mL of 5% aqueous sodium carbonate, and two 300-mL portions of water. After the extracts are dried (anhydrous sodium sulfate), the pale yellow filtrate is evaporated to give 11.9-12.4 g of crude 9-thiabicyclo[3.3.1]nonane-2,6-dione (**3**) as a slightly yellow solid. Thin layer chromatography (silica/dichloromethane) indicates the presence of a small quantity of colored polar impurity, which is not easily removed by recrystallization. The crude solid is dissolved in ca. 300 mL of hot 1:1 ethyl ether/benzene containing 0.5 g of activated charcoal, then filtered through a short plug of Celite filter aid. The plug is washed with further hot solvent and the combined filtrates are evaporated to give 11.3-11.7 g (88-92%) of 9-thiabicyclo[3.3.1]nonane-2,6-dione (**3**) as a faintly off-white solid of ca. 99% purity. Analytically pure material is obtained by recrystallization from 2:1 light petroleum/chloroform or from 1:1 light petroleum/dichloromethane.

Alternatively, the product is sublimed under reduced pressure (ca. 160°C/30 mm) (Note 12).

2. Notes

1. A magnetic stirring bar may be used provided that *vigorous* mixing of the solution is possible.

2. 1,5-Cyclooctadiene purchased from the Aldrich Chemical Company, Inc. was purified by elution of the neat liquid through a short column of activated alumina immediately prior to use.

3. Sulfur dichloride partially decomposes on standing to chlorine and sulfur monochloride and so should always be purified before use. Commercial sulfur dichloride of approximately 80% purity (Aldrich Chemical Company, Inc.) was purified in a hood following the procedure described by Brauer.² Phosphorus trichloride (2 mL) was added to crude sulfur dichloride (200 mL) contained in a flask set up for a standard distillation and protected from the atmosphere by a silica gel drying tube. The fraction boiling between 55-63°C was collected in a receiving flask containing phosphorus trichloride (5 drops). A second distillation using the same technique gave pure sulfur dichloride of bp 59-60°C/atmospheric pressure. Material stabilized with a few drops of phosphorus trichloride may be stored for a few days in a sealed container without significant decomposition.

4. Compound **1** has the following spectral properties. IR (paraffin mull) cm^{-1} : 1245 (m), 1160 (m), 1000 (w), 950 (w), 890 (w), 815 (s), 755 (m), 735 (m); ^1H NMR (CDCl_3) δ : 2.18-2.38 (6 H, m), 2.65-2.70 (2 H, m), 2.85-2.88 (2 H, m), 4.68-4.75 (2 H, m); ^{13}C NMR (CDCl_3) δ : 28.3 (t), 32.6 (t), 37.3 (d), 62.5 (d). The crude product is sufficiently pure for most purposes, but analytically pure material is colorless, lit.³ mp 98.1-99.6°C. This may be obtained by trituration of the crude product with a little ethyl

ether (which removes a small quantity of yellowish oil) followed by filtration. Alternatively it may be purified by sublimation under reduced pressure (48°C/0.05 mm)³ or recrystallized from benzene.⁴

5. The checkers employed anhydrous sodium carbonate.

6. The checkers filtered the solution at this point to remove small amounts of a brown solid.

7. (endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol (**2**) is remarkably insoluble in the solvents normally used for extraction of organic materials from aqueous solutions.

8. Compound (**2**) has the following spectral properties. IR (paraffin mull) cm^{-1} : 3300 (s), 1025 (s), 990 (m), 950 (w), 900 (w), 880 (m); ^1H NMR (d^6 -DMSO) δ : 1.55-1.93 (6 H, m), 2.28-2.50 (4 H, m), 3.91 (2 H, m), 4.91 (2 H, d, $J = 6$); ^{13}C NMR (d^6 -DMSO) δ : 26.4 (t), 30.8 (t), 37.0 (d), 70.7 (d).

9. Lautenschlaeger⁵ has reported that diol **2** can be obtained in polymorphic forms with melting points between 188°C and 257°C according to the history of the sample. Determination of the mp is therefore not necessarily a good indicator of purity in this particular case, and the spectroscopic methods quoted are recommended. Crystals from methanol had mp 250-253°C (lit.⁴ 249-250.5°C) but these rapidly became opaque and eventually crumbled to a white powder with lower mp. Samples of diol **2** prepared by the method described here melted indistinctly about 220-225°C.

10. Dimethyl sulfoxide was stirred and heated at ca. 100°C with powdered calcium hydride for 2 hr, distilled under reduced pressure, and used at once.

11. Care must be taken to ensure that the liquid from the funnel drops directly into the reaction and not onto the walls of the flask where it will solidify.

12. The physical properties of the product are as follows: mp 140-142°C; lit.⁶ 140-142°C. IR (paraffin mull) cm^{-1} : 1690 (s), 1260 (m), 1215 (m), 1125 (m), 1095 (w), 1035 (w), 935 (w); ^1H NMR (CDCl_3) δ : 2.47-2.69 (6 H, m), 2.82-2.89 (2 H, m), 3.37-3.38 (2 H, m); ^{13}C NMR (CDCl_3) δ : 31.1 (t), 36.6 (t), 44.7 (d), 205.2 (s).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

The addition of sulfur dichloride and 1,5-cyclooctadiene to produce (1 α ,2 α ,5 α ,6 α)-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (1) has been described by several workers.^{3-5,7} Determination of the stereochemistry of the product has been carried out using ^1H NMR methods,³ and by means of the X-ray crystal structure of the corresponding sulfone derivative.⁸ The procedure described here as step A is that due to Corey and Block.³

Hydrolysis of the dichloride (1) to yield (endo,endo)-9-thiabicyclo[3.3.1]nonane-2,6-diol (2) has been carried out using water,⁴ aqueous sodium hydroxide,⁴ aqueous sodium hydrogen carbonate,⁵ and aqueous sodium carbonate.⁵ Step B is an improved version of the latter reaction. The (endo,endo)-stereochemistry was originally inferred from IR evidence,⁴ and subsequently confirmed by NMR work and the crystal structure of the related compound 2,6-dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxide.⁹ Both the high lability of the dichloride (1) and the stereochemistry resulting from hydrolysis arise from neighboring group participation of the sulfur atom

to form intramolecular sulfonium ion intermediates.^{3,4} These processes have been studied in detail by Vincent and co-workers¹⁰ using ¹³C NMR spectroscopy.

The diketone (3) is a versatile intermediate for the preparation of 9-thiabicyclo[3.3.1]nonane derivatives^{6,11-13} and provides a simple synthetic entry to a number of other heterocycles such as the 2-thiaadamantane,^{13,14} thiacyclohexane,¹⁵ thiacycloheptane,¹⁵ 2,6-dithiaadamantane,¹⁶ and 2-thiabrexane¹⁷ ring systems. Only one previous procedure for its preparation has been published.⁶ This method involves the oxidation of diol (2) with chromium trioxide in pyridine and dichloromethane to yield 9-thiabicyclo[3.3.1]nonane-2,6-dione (3) in 65% yield. In practice this reaction is difficult to carry out reproducibly because of precipitation of tarry chromium salts which make adequate stirring and extraction of the product very difficult. Consequently the dione (3) is often accompanied by partly oxidized material and/or material where the sulfur atom has been oxidized. The method reported here avoids these technical difficulties and affords a considerably increased yield.

More generally, the procedure described in step C illustrates how the Swern oxidation method¹⁸⁻²⁰ can be employed for the selective oxidation of an alcohol functionality in the presence of a sulfur moiety. A drawback of the original Swern oxidation is the lack of solubility of some substrates in the dichloromethane solvent at low temperatures, which results in a serious reduction of yield. In the past this has been avoided by carrying out the oxidation step at -10°C. This once again gave excellent yields, but this procedure required the use of twice the stoichiometric amount of oxidant.¹⁹ The method described here as step C demonstrates that this is not necessary, and that the oxidation of insoluble materials can be carried out following the routine procedure provided that the substrate is added as a solution in dry dimethyl sulfoxide.

Step C has been carried out on three times the described scale without any deleterious effects being noted.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

9-Thiabicyclo[3.3.1]nonane-2,6-dione (9); (37918-35-7)

(1 α ,2 α ,5 α ,6 α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (9); (10502-30-4)

1,5-Cyclooctadiene: 1,5-Cyclooctadiene, (Z,Z)- (8,9); (1552-12-1)

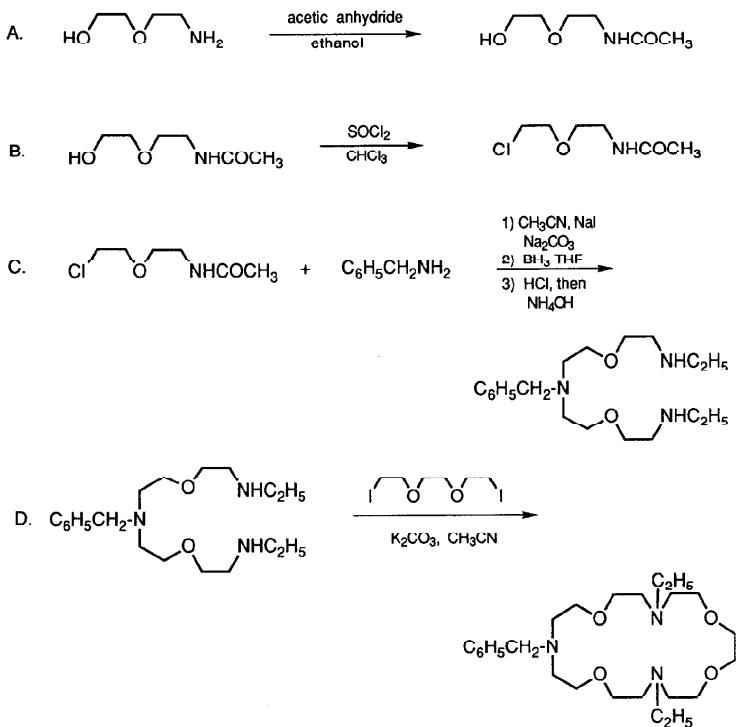
Sulfur dichloride: Sulfur chloride (8,9); (10545-99-0)

(endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol: 9-Thiabicyclo[3.3.1]nonane-2,6-diol stereoisomer (8,9); 9-Thiabicyclo[3.3.1]nonane-2,6-diol, (endo,endo)- (10); [22333-35-3]

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)

4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE (TRIAZA-21-CROWN-7)



Submitted by Krzysztof E. Krakowiak¹ and Jerald S. Bradshaw.²

Checked by Hyunik Shin and James D. White.

1. Procedure

A. *N*-[2-(2-Hydroxyethoxy)ethyl]acetamide. Into an oven-dried, 100-mL, three-necked, round-bottomed flask that contains a magnetic stirring bar, 25-mL addition funnel, condenser, and thermometer, is placed 15.75 g (0.15 mol) of 2-(2-aminoethoxy)ethanol (Note 1) in 20 mL of anhydrous ethanol (Note 2). Acetic anhydride (15.75 g, 0.154 mol) (Note 1) is slowly dripped into this stirring solution while the temperature is kept at or below 40°C. The resulting mixture is stirred under reflux for 15 min. The mixture is evaporated on a rotary evaporator to give a pale yellow oil that is distilled through a short path apparatus containing a 2-cm Vigreux column to give 20.3-21.5 g (92-97%) of product, bp 135-139°C/0.12 mm (Note 3).

B. *N*-[2-(2-Chloroethoxy)ethyl]acetamide. *N*-[2-(2-Hydroxyethoxy)ethyl]-acetamide (20.58 g, 0.14 mol) in 30 mL of chloroform (Note 4) is placed in an oven-dried, 250-mL, three-necked, round-bottomed flask that contains a magnetic stirring bar, pressure-equalizing dropping funnel, condensor that is connected by a polyethylene tube to a glass funnel, and a thermometer (Note 2). The flask is cooled in an ice bath and the glass funnel is immersed in a beaker of water. Thionyl chloride (26 g, 0.24 mol) (Note 1) in 25 mL of chloroform is added dropwise to the stirring mixture at 10-15°C. The mixture is then stirred at room temperature for 30 min and under reflux for 20 min (Note 5). It is immediately cooled to 30°C and the solvent and excess thionyl chloride are removed on a rotary evaporator (Note 6). The residue is immediately distilled through an 8-cm Vigreux column using an oil bath (Note 7) to give 17-18 g (73-77%) (Note 8) of *N*-[2-(2-chloroethoxy)ethyl]acetamide, bp 105-108°C/0.1 mm (Note 3).

C. *9-Benzyl-3,9,15-triaza-6,12-dioxahexadecane*. A mixture of 17.5 g (0.105 mol) of *N*-[2-(2-chloroethoxy)ethyl]acetamide, 200 mL of acetonitrile (Note 9), 22 g (0.21 mol) of anhydrous sodium carbonate (Note 10), 16.5 g (0.11 mol) of sodium

iodide (Notes 1 and 11) and 5.35 g (0.05 mol) of benzylamine (Note 1) is added to an oven-dried, 250-mL, three-necked flask that contains a magnetic stirring bar and condenser. The mixture is refluxed for 48 hr, cooled to room temperature and filtered under vacuum. The solid in the filter is washed twice with 70-mL portions of methylene chloride (Note 12). The combined filtrate and methylene chloride mixture are evaporated on a rotary evaporator until all of the solvents are removed. The residue is dissolved in 70 mL of water and transferred to an extraction funnel. The aqueous solution is extracted with three 200-mL portions of methylene chloride (Note 12). The combined methylene chloride extracts are dried over anhydrous magnesium sulfate (Note 13). The mixture is filtered under vacuum and the solid is washed with 100 mL of methylene chloride. The solvents are evaporated on a rotary evaporator. The residue is dissolved in 80 mL of tetrahydrofuran (Note 14) and transferred to a dropping funnel equipped with an anhydrous calcium sulfate drying tube. This solution is slowly dripped into 300 mL of cold, stirring 1 N borane-THF (Notes 1 and 15) in an oven-dried, 1-L, one-necked, round-bottomed flask containing a magnetic stirring bar. The addition funnel is removed, a condenser equipped with an anhydrous calcium sulfate drying tube is connected, and the stirring mixture is refluxed for 16 hr. The mixture is cooled and 20 mL of distilled water is slowly dripped into it from a dropping funnel (Note 16). The solvents are then removed on a rotary evaporator. The residue is cooled in an ice water bath and 300 mL of aqueous 18% hydrochloric acid (Note 17) is slowly added to the stirring mixture. The resulting mixture is stirred for 16 hr, first at room temperature, and then warmed until the solvent just reaches the boiling point. The solution is cooled and the solvents are completely removed on a rotary evaporator. To the residue is added 50 mL of water. The aqueous mixture is stirred (Note 18) and filtered under vacuum. The solid is washed with 15 mL of water, and 150 mL of ammonium hydroxide (Note 19) is added to the filtrate (Note 2). The resulting solution is extracted three times with 300-mL portions of chloroform (35 g of

sodium chloride is added to the aqueous solution before the third extraction). The chloroform layers are combined and dried over anhydrous magnesium sulfate. The solution is filtered under vacuum, the solid is washed with 50 mL of chloroform, and the solvent is removed on a rotary evaporator. The residue is distilled slowly through a short path apparatus that contains a 2-cm Vigreux column to give 11.6-12.6 g (69-75%) of 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane as a light yellow oil, bp 144°-152°/0.085 mm (Note 3).

D. 4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (triaza-21-crown-7). A mixture of 10 g (0.03 mol) of 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane and 600 mL of acetonitrile (Note 9) is placed in an oven-dried, 1-L, three-necked, round-bottomed flask equipped with a condenser, an efficient mechanical stirrer and a rubber septum. Argon gas is flushed through the flask using a needle through the septum before and during the reaction. To the above mixture, while stirring at room temperature, is added 50 g (0.36 mol) of anhydrous powdered potassium carbonate (Note 20) and the mixture is stirred for 15 min; then 11.5 g (0.031 mmol) of 1,2-bis(2-iodoethoxy)ethane (Note 1) is added. The resulting mixture is stirred under reflux for 24 hr. The cooled mixture is filtered under vacuum and the solid is washed with 100 mL of acetonitrile. The solvent is removed from the filtrate on a rotary evaporator. Methylene chloride (160 mL) (Note 12) is added to the residue and the resulting mixture is stirred (Note 18). The mixture is filtered under vacuum and the solid is washed with two 20-mL portions of methylene chloride (Note 12). The combined organic layers are evaporated on a rotary evaporator to give a brown oil. The oil is purified by chromatography on 300 g of alumina (Note 21) using 1000 mL of toluene/ethanol: 50:1 as the eluant. The first 120-150 mL of eluant is removed. The remainder of the eluant is evaporated in a rotary evaporator to give 9.6-10 g (72-75%) of the triaza-21-crown-7 as a light yellow oil (Notes 22-24).

2. Notes

1. 2-(2-Aminoethoxy)ethanol, acetic anhydride (99+%), thionyl chloride (99+%), benzylamine (99%), 1,2-bis(2-iodoethoxy)ethane (98%), anhydrous sodium iodide (99+%) and borane-tetrahydrofuran complex (1.0 M solution in tetrahydrofuran) were purchased from Aldrich Chemical Company, Inc. and were used without further purification.

2. The reaction must be carried out in an efficient hood.

3. The IR and NMR spectra in reference 3 were consistent with the proposed structure.

4. Chloroform ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.

5. The reaction also can be carried out at room temperature for 48 hr.

6. A rotary evaporator that has a safety flask in the vacuum line was used. The water bath temperature was not higher than 50°C.

7. The submitters prefer to use an oil bath rather than a heating mantle because control of pot temperature is essential so that no polymers can form. There is a loss of vacuum at the beginning of the distillation because of various gases in the product.

8. The yield from a seven times larger reaction was 85%.³

9. Acetonitrile ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.

10. Sodium carbonate (anhydrous A.C.S. certified) distributed by Fisher Scientific was used.

11. In reference 3, xylene was used as the solvent instead of acetonitrile and sodium iodide was not used. The yield in that case was lower.

12. Methylene chloride ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.

13. Magnesium sulfate (anhydrous, powder) distributed by EM Science was used.

14. Tetrahydrofuran (HPLC quality), manufactured by Mallinckrodt Inc., was used.

15. When fresh lithium aluminum hydride was used instead of the borane-tetrahydrofuran complex,³ the reduction gave low yields and the product was more difficult to purify.

16. The first drops of water are added very slowly because the reaction causes considerable foaming.

17. Analytical reagent grade hydrochloric acid, manufactured by Mallinckrodt Inc., was used for the preparation of the 18% solution.

18. The mixture was stirred until the solid was completely suspended.

19. Analytical reagent grade ammonium hydroxide ($\text{NH}_3 = 29.6\%$), manufactured by Mallinckrodt Inc., was used.

20. "Baker Analyzed" reagent grade potassium carbonate (anhydrous, granular) was used.

21. Activated, neutral, 150 mesh alumina (Brockman 1 standard grade), sold by Aldrich Chemical Company, Inc., was used in a 5-cm diameter column for the purification of the triaza-crown. Alumina TLC plates (Aluminum oxide 60F254 neutral (Type E), manufactured by E. Merck, distributed by EM Science) were used to monitor the purification process (toluene/ethanol = 20:1, using iodine as an indicator).

22. The product is nearly 98% pure as determined by GC using a Carlo Erba 5160 Mega instrument, flame ionization detection, with H_2 as the carrier gas (50 cm/sec). The column was a 10-m x 200- μm i.d. fused silica column coated at a 0.15- μm film thickness with SE-33 (methyl silicone). The split injector was kept at 300°C,

the detector at 280°C, and the column at 230°C. The product gave the correct elemental analysis and has the following spectral properties: ¹H NMR (CDCl₃, 200 MHz) δ: 1.0 (t, 6 H), 2.55 (m, 4 H), 2.72 (m, 12 H), 3.6 (m, 18 H), 7.35 (m, 5 H); IR (neat) cm⁻¹: 2860, 1440, 1340, 1110; MS (20 eV) m/e 160, 275, 336, 451 (100%).

23. The crown can be distilled under high vacuum in a short path distillation apparatus using an oil bath, bp 100-190°C/0.05 mm.

24. The product should be stored under argon at 0°C in a dark bottle to prevent decomposition.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

The procedure described here illustrates a new "building block" method for the preparation of per-N-alkyl-substituted polyaza-crown compounds.³⁻⁵ The key building block, N-[2-(2-chloroethoxy)ethyl]acetamide and its benzamide analog,³ allows the preparation of a variety of tri- and tetraamino compounds capable of ring closure reactions to form a variety of polyaza-crowns.^{3,4} Polyaza-crowns containing a secondary amine side chain (mono lariat ether),⁵ a hydroxyalkyl side chain,⁶ and very large polyaza-crowns (30-36 ring members)³ have been prepared using these procedures. The triaza-18-crown-6 analog was prepared in an overall yield of 25% by treating 9-benzyl-3,9,15-triaza-6,12-dioxahaptadecane with 3-oxapentanedioyl dichloride followed by reduction.^{3,4}

The procedures previously used to prepare N-peralkylated polyaza-crowns required the use of nitrogen protecting groups that must subsequently be removed and the alkyl groups added.⁷⁻¹¹ These added steps greatly reduced the overall yields of the polyaza-crowns. Polyaza-crowns are important for complexing certain "soft" heavy metals,¹²⁻¹⁶ and anions,¹⁷⁻²⁰ and as enzyme mimics in certain biological systems.²¹ It is important to note that the N-peralkylated polyaza-crowns have about the same affinity for metal cations as the unsubstituted aza-crowns.¹⁵ We have prepared 26 new N-peralkylated polyaza-crowns using this new method.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-[2-(2-Hydroxyethoxy)ethyl]acetamide: Acetamide, N-[2-(2-hydroxyethoxy)ethyl]- (12); (118974-46-2)

2-(2-Aminoethoxy)ethanol: Ethanol, 2-(2-aminoethoxy)- (8,9); (929-06-6)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

N-[2-(2-Chloroethoxy)ethyl]acetamide: Acetamide, 2-(2-chloroethoxy)-N-ethyl- (9); (36961-73-6)

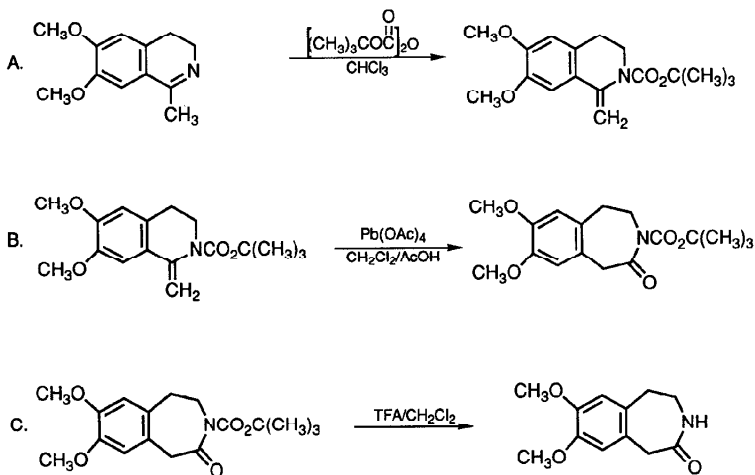
Thionyl chloride (8,9); (7719-09-7)

Benzylamine (8); Benzenemethanamine (9); (100-46-9)

Boran-Tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1:1) (8,9); (14044-65-6)

1,2-Bis(2-Iodoethoxy)ethane: Ethane, 1,2-bis(2-iodoethoxy)- (9); (36839-55-1)

**TETRAHYDRO-3-BENZAZEPIN-2-ONES: LEAD TETRAACETATE
OXIDATION OF ISOQUINOLINE ENAMIDES**



Submitted by George R. Lenz and Ralph A. Lessor.¹

Checked by Shaowo Liang and Leo A. Paquette.

1. Procedure

A. N-(tert-Butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline. A 1-L, three-necked, round-bottomed flask is equipped with a thermometer, magnetic stirring bar, nitrogen inlet with gas bubbler, and a pressure-equalizing dropping funnel (Note 1). The flask is charged with 102.6 g (500 mmol) of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (Note 2) and 150 mL of alcohol-free

chloroform (Note 3). The mixture is warmed to 50°C with stirring. The dropping funnel is charged with a solution of 136.9 g (627 mmol) of di-*tert*-butyl pyrocarbonate (Note 4) in 50 mL of alcohol-free chloroform. The nitrogen is turned off, and the solution of di-*tert*-butyl pyrocarbonate is added to the mixture at such a rate as to maintain steady but controlled gas evolution (Note 5). The stirred reaction mixture is heated at 60–65°C until gas evolution ceases, then allowed to cool to room temperature with stirring.

Solvent is removed on a rotary evaporator at reduced pressure, and the resulting crude pink solid is dried overnight under high vacuum. The yield of slightly pink solid is 176.5–180 g (Notes 6, 7).

B. N-(tert-Butoxycarbonyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one. A 1-L, three-necked, round-bottomed flask is equipped with a nitrogen inlet, mechanical stirrer, thermometer, and a pressure-equalizing dropping funnel (Note 8). The flask is charged with 93 g (210 mmol) of lead tetraacetate (Note 9) and 250 mL of glacial acetic acid. Stirring is started, the flask is immersed in an ice-water bath, and the funnel is charged with a solution of 61 g (200 mmol) of *N*-(*tert*-butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (Note 10) in 250 mL of methylene chloride. This solution is added at such a rate that a temperature of 19–23°C is maintained throughout the addition, typically over a period of 15 to 20 min. The cooling bath is removed, and the mixture is stirred at room temperature for 1 hr. Glycerol (4 mL) is added to quench unreacted lead tetraacetate, and the mixture is stirred for an additional 10 min.

The mixture is poured into 750 mL of water in a 2-L separatory funnel and shaken thoroughly. The phases are separated, and the aqueous phase is extracted with two 100-mL portions of methylene chloride. The combined organic layers are washed with 700 mL of water, followed by successive 100-mL portions of saturated aqueous sodium bicarbonate until no further effervescence is observed. The organic layer is dried over magnesium sulfate, filtered, and evaporated at reduced pressure to

give a yellow-orange solid, which is dissolved in 100 mL of boiling acetone and allowed to cool slowly to room temperature, then kept overnight at -20°C. Filtration affords a cream-colored solid in a yield of 51.2-52.2 g (Notes 11, 12). A second crop is obtained by evaporation of the mother liquors, dissolution in a minimal amount of boiling acetone, cooling and seeding. The total yield is brought to 58-59 g (90-92%).

C. 7,8-Dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, and pressure-equalizing dropping funnel. The flask is charged with 32.1 g (100 mmol) of recrystallized N-(tert-butoxycarbonyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 100 mL of methylene chloride. The flask is immersed in an ice-water bath and stirred until the internal temperature reaches 5°C. The dropping funnel is charged with 40 mL of trifluoroacetic acid, which is added dropwise at a rate such that the temperature of the reaction mixture does not exceed 10°C (Note 13). When addition is complete, the cooling bath is removed, and the mixture is stirred for 3 hr (Note 14).

The mixture is diluted with an additional 700 mL of methylene chloride and poured into a separatory funnel containing 500 mL of water. The funnel is shaken thoroughly, and the phases are separated. The organic layer is washed with 500 mL of water, followed by successive washes with 200-mL portions of saturated aqueous sodium bicarbonate until no further effervescence is observed (Note 15). The organic phase is dried over sodium sulfate and evaporated under reduced pressure to give 24.8-25.2 g of crude product. The crude material is dissolved in a minimal amount of boiling methylene chloride, and then diluted with an equal volume of ethyl acetate. The mixture is boiled down to approximately two thirds of its starting volume, by which time crystallization has begun, then allowed to cool slowly to room temperature. After storage at -20°C overnight, filtration affords 17.5-18.0 g (79-81%) of product, mp 194-195°C (Notes 16, 17).

2. Notes

1. The glassware is dried in an oven at 110°C and assembled while still hot, then allowed to cool while a slow stream of nitrogen is passed through the apparatus.

2. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline was prepared according to an *Organic Syntheses* procedure: Drossi, A.; Dolan, L. A.; Teitel, S. *Org. Synth., Coll. Vol. VI* 1988, 1.

3. The submitters used J. T. Baker Chemical Company hydrocarbon-stabilized chloroform containing 0.015% amylene stabilizer. The checkers used chloroform of comparable quality purchased from Aldrich Chemical Company, Inc.

4. The submitters used commercially available tert-butyl pyrocarbonate from either Fluka or Aldrich Chemical Company, Inc. Alternatively, the reagent can be prepared according to Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Org. Synth., Coll. Vol. V* 1988, 418.

5. The addition typically took 1.5 to 2 hr. The bubbler on the nitrogen line used to flush the flask is conveniently used to monitor the evolution of carbon dioxide as the reaction proceeds.

6. This material is pure enough for use in the next step. The impurities of tert-butyl alcohol and a small amount of unreacted tert-butyl pyrocarbonate do not interfere with the oxidation.

7. If desired, the material can be recrystallized from methanol; under these circumstances, 146-149 g of white solid, mp 101-102°C, is returned. The spectral characteristics of recrystallized material are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.49 (s, 9 H), 2.78 (t, 2 H, $J = 5.9$), 3.77 (t, 2 H, $J = 5.9$), 3.86 (s, 3 H), 3.89 (s, 3 H), 5.31 (s, 1 H), 5.50 (s, 1 H), 6.56 (s, 1 H), 7.11 (s, 1 H); IR (KBr) cm^{-1} : 1690, 1630, 1605, 1510, 1390, and 1170; ^{13}C NMR (75 MHz, CDCl_3) δ : 28.38, 28.96, 43.51, 55.89, 56.02, 80.47, 101.86, 107.46, 110.77, 124.84, 127.72, 139.99, 147.51, 149.22, 153.83.

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.02; H, 7.48; N, 4.65.

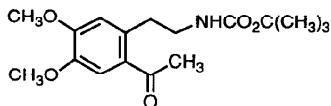
8. The glassware is assembled hot under nitrogen as for the previous step. The nitrogen inlet and stirrer are mounted on a Claisen adapter, and the thermometer is removed during the flushing period, then reinserted.

9. The submitters used lead tetraacetate from Aldrich Chemical Company, Inc., which was dried under reduced pressure at room temperature for 10 min prior to use to remove any acetic acid present. Alternatively, lead tetraacetate still containing acetic acid may be used successfully if a slight excess is used.

10. If crude material containing tert-butyl alcohol and unreacted pyrocarbonate is used in this step, the amount of starting material present is calculated based on the mass balance for the first step, assuming a quantitative conversion, and 1.05 equivalents of lead tetraacetate are used. The checkers used only pure material and advise against carrying forward less pure carbamate.

11. This material may be used directly in the following step. If desired, the material can be recrystallized from acetone, mp 116.5-118°C. The spectral characteristics of the recrystallized material are as follows: 1H NMR (300 MHz, $CDCl_3$) δ : 1.52 (s, 9 H), 3.14 (t, 2 H, $J = 6.0$), 3.84 (s, 6 H), 3.92 (s, 2 H), 4.18 (t, 2 H, $J = 6.0$), 6.56 (s, 1 H), 6.57 (s, 1 H); IR (KBr) cm^{-1} : 1715, 1610, 1525, 1370, 1255, 1110, and 1060; ^{13}C NMR (75 MHz, $CDCl_3$) δ : 28.03, 32.83, 43.42, 45.21, 55.94, 55.97, 83.18, 113.25, 114.28, 121.92, 127.09, 147.41, 148.38, 152.08, 171.33. Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.36; H, 7.30; N, 4.16.

12. If insufficient lead tetraacetate is used in the oxidation, unoxidized starting enamide is hydrolyzed during the workup to tert-butyl 2-(2-acetyl-3,4-dimethoxyphenyl) ethyl carbamate, mp 111.5-112.5°C (cf. Note 2): 1H NMR (270 MHz,



CDCl_3 δ : 1.42 (s, 9 H), 2.58 (s, 3 H), 3.03 (t, 2 H), 3.37 (q, 2 H), 3.92 (s, 3 H), 6.76 (s, 1 H), 7.23 (s, 1 H); IR (FTIR) cm^{-1} : 1707, 1674, 1604, 1517, 1266, 1212, 1152. Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_5$: C, 63.13; H, 7.79; N, 4.33. Found: C, 63.24; H, 7.91; N, 4.28. The hydrolyzed material co-migrates with the oxidation product in a variety of TLC systems, and also co-crystallizes with it. It is, however, removed during the trifluoroacetic acid (TFA) cleavage to form the bonzazepinone (Step C). The presence of any hydrolyzed material is readily detected by the presence of the acetyl resonance (δ 2.58) in the NMR spectrum.

13. After approximately 25 ml of the trifluoroacetic acid have been added, gas evolution begins. This can be quite vigorous if the temperature is not kept below 10°C .

14. The progress of the reaction can be monitored by thin layer chromatography on silica gel plates, using a 95:5:0.5 mixture of chloroform:methanol:concentrated ammonium hydroxide as the developing solvent.

15. Foaming can be quite vigorous, especially if the reaction mixture is not washed first with water prior to the use of sodium bicarbonate solution.

16. A small second crop of impure material can be obtained from the mother liquors.

17. The product exhibited the following spectral characteristics: ^1H NMR (300 MHz, CDCl_3) δ : 3.03 (t, 2 H, $J = 6.0$), 3.52-3.60 (m, 2 H), 3.75 (s, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.34 (br s, 1 H), 6.59 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 33.03, 40.62, 41.71, 55.77 (2C), 112.96, 113.53, 123.19, 128.39, 147.09, 147.72, 174.49; IR (KBr) cm^{-1} : 1675, 1220, 1125, 1100, and 1010.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

This procedure illustrates a general route to tetrahydro-3-benzazepin-2-ones from readily available dihydroisoquinolines.² The benzazepine ring system exists in various classes of isoquinoline-derived alkaloids,³ while other members of this class are being developed as pharmaceutical agents.⁴ The present procedure takes advantage of ready formation of enamides from dihydroisoquinolines and carboxylic acid anhydrides, acid chlorides, carbonic anhydrides and chlorides and their facile oxidation to differentially functionalized benzazepinones (Table 1). The mechanism has been described and involves migration of the isoquinoline aromatic ring to the exocyclic methylene group.²

Several approaches to the synthesis of the tetrahydrobenzazepine ring system have been described,⁵ and excellent methods exist for the preparation of aryl substituted tetrahydrobenzazepines.⁴ However, benzazepines that are either unsubstituted or alkyl-substituted on the azepine ring are much less readily obtainable. For instance, the benzazepinone, synthesized by this procedure, was originally isolated, in low yield, from the mixture of photoproducts obtained from the irradiation of N-[3-(3,4-dimethoxyphenyl)]propyl chloroacetamide.⁶ Preparative approaches to the benzazepinones have required multiple steps starting from an N-phenylethylacetamide and involving chloromethylation, cyanide displacement, nitrile solvolysis, hydrolysis to the amino acid and cyclization.⁷ The 1-alkyl derivatives are

subsequently prepared by alkylation of the parent compound.⁸ The current procedure reduces the preparation of the tetrahydrobenzazepinone ring system to two straightforward steps.

Ring expansion of the isoquinoline enamides is insensitive to the type of acyl functionality used to form the enamide.⁹ The reaction occurs when the isoquinoline aromatic ring is unsubstituted, or contains electron releasing substituents. The reaction is sensitive, however, to the degree and type of substitution on the exocyclic methylene group. Oxidative ring expansion occurs when the double bond is either unsubstituted or monoalkyl substituted. Phenyl substitution yields differing products depending on a number of variables.⁹ When the exocyclic double bond is disubstituted, oxidation with lead tetraacetate proceeds readily, but does not lead to ring expansion.¹⁰ The ring expansion reaction works equally well for the preparation of tetrahydrobenzazocinones from tetrahydrobenzazepine enamides (Table 2).¹¹

The acid-catalyzed cleavage of the tert-butoxycarbonyl group is the best method to form the parent benzazepinone. Other methods used have been the Pd/C hydrogenolysis of a benzyloxycarbonyl group,^{2,11,12} and zinc mediated reductive cleavage of trichloroethoxy and trichloro-tert-butoxy carbonyl groups.¹¹

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Table 1
Lead Tetraacetate Oxidative Ring Expansion
of Isoquinoline Enamides

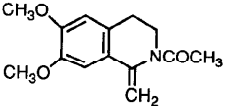
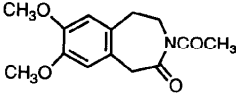
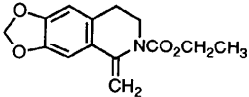
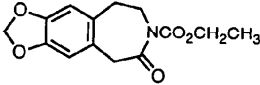
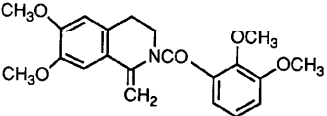
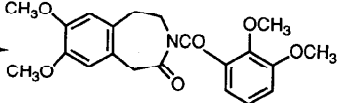
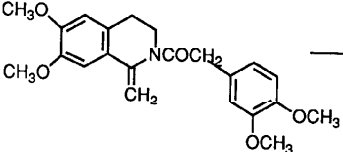
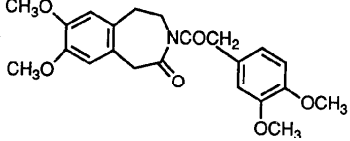
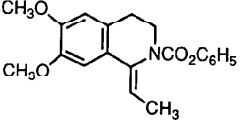
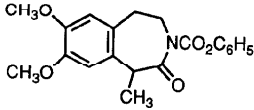
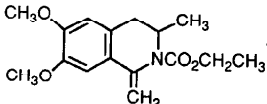
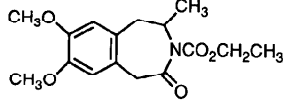
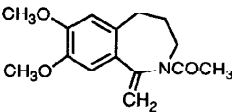

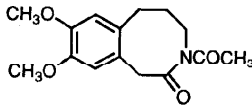
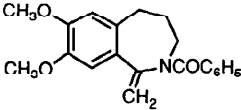

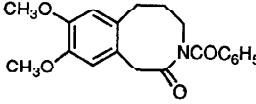
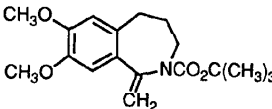

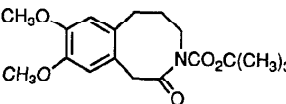
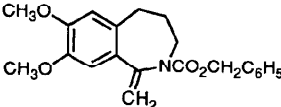

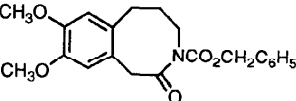
		Yield (%) 62
		91
		92
		94
		50
		72

Table 2

Lead Tetraacetate Oxidative Ring Expansion
of Benzazepine Enamides

			Yield(%) 76
			83
			73
			78

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-(tert-Butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline:

2(1H)-Isoquinolinecarboxylic acid, 3,4-dihydro-6,7-dimethoxy-1-methylene,
1,1-dimethylethyl ester (11); (82044-08-4)

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline: Isoquinoline, 3,4-dihydro-6,7-
dimethoxy-1-methyl- (8,9); (4721-98-6)

Di-tert-butyl pyrocarbonate: Formic acid, oxydi-, di-tert-butyl ester (8); Dicarboxylic acid,
bis(1,1-dimethylethyl) ester (9); (24424-99-5)

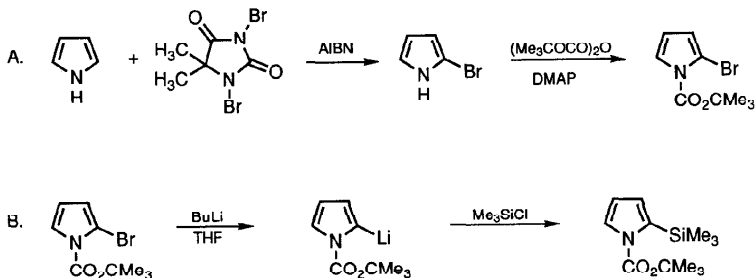
Lead tetraacetate: Acetic acid, lead (4+) salt (8,9); (546-67-8)

Glycerol (8); 1,2,3-Propanetriol (9); (56-81-5)

7,8-Dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one: 2H-3-Benzazepin-2-one,
1,3,4,5-tetrahydro-7,8-dimethoxy- (8,9); (20925-64-8)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

**2-SUBSTITUTED PYRROLES FROM N-tert-BUTOXYCARBONYL-
2-BROMOPYRROLE: N-tert-BUTOXY-2-TRIMETHYLSILYLPYRROLE**



Submitted by Wha Chen, E. Kyle Stephenson, Michael P. Cava,¹ and
Yvette A. Jackson ²
Checked by Wei He and Leo Paquette.

1. Procedure

A. *N*-tert-Butoxycarbonyl-2-bromopyrrole. A dry, 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two solid addition funnels, and a three-way stopcock attached to a balloon filled with nitrogen. To the flask are added 4.5 g (67.2 mmol) of pyrrole (Note 1) and 180 mL of tetrahydrofuran (Note 2). The flask is evacuated and purged with nitrogen (Note 3). The stirred solution is cooled to -78°C with a dry ice-acetone bath (Note 4) and a catalytic amount (ca. 0.1 g) of azoisobutyronitrile (AIBN) (Note 5) is added via solid addition funnel. After 5 min, 9.57 g (33.6 mmol) of 1,3-dibromo-5,5-dimethylhydantoin (Note 6) is added over a 20-min period via solid addition funnel. The light-green mixture is stirred for an additional 10

min, then allowed to stand for 2 hr, keeping the temperature below -50°C . The solution is filtered by suction into a dry, 500-mL, round-bottomed flask that has been cooled to -78°C in a dry ice-acetone bath. The flask is equipped with a magnetic stirring bar and a three-way stopcock attached to a balloon filled with nitrogen. To the stirred dark-green solution is added 2.71 g (26.9 mmol) of triethylamine followed immediately by addition of 20.4 g (93.9 mmol) of di-*tert*-butyl dicarbonate and a catalytic amount (ca. 0.1 g) of 4-dimethylaminopyridine (Note 7). The flask is evacuated and purged with nitrogen (Note 3). The mixture is stirred for 8 hr while it is allowed to warm to room temperature (Note 8). The solvent is removed under reduced pressure at room temperature and 100 mL of hexane is added to the crude product, which is washed with deionized water (3 x 100 mL), dried over sodium sulfate, and concentrated under reduced pressure at room temperature. The crude product is purified by chromatography on amine-treated neutral silica (270 g) using hexane as the eluent (Note 9). The fractions containing the product are identified by TLC, combined, and concentrated under reduced pressure at room temperature to yield compound **1** as a colorless oil (13.5-14.7 g, 82-89%) (Note 10).

B. *N*-*tert*-Butoxycarbonyl-2-trimethylsilylpyrrole. A solution of *N*-*tert*-butoxycarbonyl-2-bromopyrrole (13.5 g, 54.9 mmol) in 40 mL of hexane is added to 200 mL of tetrahydrofuran (Note 2) in a dry, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a three-way stopcock attached to a balloon of nitrogen. The flask is evacuated and purged with nitrogen (Note 3). The stirred mixture is cooled to -78°C and 34.3 mL of 1.6 M butyllithium in hexane (Note 10) is added slowly via syringe over a 10-min period, during which time the colorless solution becomes brown. After an additional 10 min, 13.4 g (124 mmol) of chlorotrimethylsilane (Note 11) in 10 mL of tetrahydrofuran (Note 3) is added via syringe over a 10-min period. Stirring is continued and the mixture is allowed to warm to -30°C over a 1-hr period. The reaction mixture is quenched with saturated aqueous

sodium bicarbonate (10 mL) at which point a dark red-purple color develops. After warming to 0°C, the solvent is removed under reduced pressure and the product is extracted into 300 mL of hexane. The organic layer is washed twice with 150 mL of water and then dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled twice using a Kugelrohr oven at 85°C and 0.15 mm to give the pure product **2** (10.5-11.1 g, 80-85%) (Note 12).

2. Notes

1. Pyrrole (Aldrich Chemical Company, Inc.) was freshly distilled before use.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl.
3. The apparatus is maintained under a nitrogen atmosphere during the course of the reaction.
4. The level of the reaction mixture must remain below the level of the cooling bath to avoid partial decomposition of the bromination product.
5. Azoisobutyronitrile (AIBN) (Fluka) was used as received.
6. Commercial 1,3-dibromo-5,5-dimethylhydantoin (Aldrich Chemical Company, Inc.) (22.0 g) was stirred for 12 hr at room temperature with 400 mL of 5% aqueous sodium bicarbonate, then stirred with 400 mL of deionized water for 8 hr, filtered, washed with 500 mL of deionized water and dried over phosphorus pentoxide to constant weight. The checkers used the commercial brominating agent as received from Aldrich Chemical Company, Inc.
7. Di-tert-butyl dicarbonate (Aldrich Chemical Company, Inc.) and 4-dimethylaminopyridine (Aldrich Chemical Company, Inc.) were used as received.
8. The checkers found that the reaction mixture must be stirred at room temperature for at least 2 hr prior to workup. It is advisable to monitor the progress of reaction by TLC.

9. The column is packed with hexane and pretreated with 500 mL of 5% triethylamine in hexane, then washed with 700 mL of hexane before addition of the compound.

10. Although this N-BOC derivative is far more stable than 2-bromopyrrole, it is best stored as a 20-25% solution in hexane at -10°C. Under these conditions, solutions show no sign of decomposition after many months. The product shows the following spectrum: ^1H NMR (CDCl_3) δ : 1.61 (s, 9 H), 6.14 (t, 1 H, $J = 3.5$), 6.29 (dd, 1 H, $J = 2.0, 3.5$), 7.30 (dd, 1 H, $J = 2.0, 3.5$).

11. Butyllithium solution (Aldrich Chemical Company, Inc.) and chlorotrimethylsilane (Aldrich Chemical Company, Inc.) were used as received.

12. The spectral properties for 2-trimethylsilyl-N-BOC pyrrole are as follows: ^1H NMR (CDCl_3) δ : 0.27 (s, 9 H), 1.60 (2, 9 H), 6.21 (t, 1 H, $J = 3.0$), 6.46 (dd, 1 H, $J = 1.5, 3.0$), 7.38 (dd, 1 H, $J = 1.5, 3.0$).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Whereas 2-lithiothiophene and 2-lithiofuran are readily prepared from butyllithium and the parent heterocycles by lithium-hydrogen exchange, a similar exchange with pyrrole affords only N-lithiopyrrole. A study of the lithium-hydrogen exchange of several N-blocked pyrroles with strong bases concluded that synthetically useful lithium hydrogen exchange at the 2-position could best be effected using as the

substrate N-tert-butoxycarbonylpyrrole, but only in conjunction with the very hindered and costly base lithium tetramethylpiperidide.³

In the present procedure, pyrrole is brominated under mild conditions to the very labile 2-bromopyrrole using 1,3-dibromo-5,5-dimethylhydantoin: the latter reagent gives better results than the previously employed N-bromosuccinimide.⁴ Direct conversion of 2-bromopyrrole to its more stable N-tert-butoxycarbonyl derivative (1) affords a substrate which readily undergoes lithium-halogen exchange with butyllithium at -78°C. Subsequent reaction with an electrophile is exemplified by the reaction with chlorotrimethylsilane to give N-tert-butoxycarbonyl-2-trimethylsilylpyrrole (2). Other electrophiles (e.g., dimethyl disulfide, methyl chloroformate) have also been employed successfully.⁵ In addition, a similar procedure has been used to convert pyrrole into N-tert-butoxy-2,5-disubstituted pyrroles.⁵

The N-tert-butoxycarbonyl protecting group of substituted pyrroles can be removed readily by methoxide ion³ or, when electron-withdrawing substituents are present, by mild thermolysis.⁶

1. Department of Chemistry, The University of Alabama, P.O. Box 870336, Tuscaloosa, AL 35487-0336.
2. Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies.
3. Hasan, I.; Marinelli, E. R.; Chang Lin, L.-C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
4. Gilow, H. W.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221.
5. Chen, W.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 6025.
6. Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-tert-Butoxycarbonyl-2-bromopyrrole: 1H-Pyrrole-1-carboxylic acid, 2-bromo-, 1,1-dimethylethyl ester (12); (117657-37-1)

N-tert-Butoxycarbonyl-2-trimethylsilylpyrrole: 1H-Pyrrole-1-carboxylic acid, 2-(trimethylsilyl)-, 1,1-dimethylethyl ester (10); (75400-57-6)

Pyrrole: 1H-Pyrrole (9); (109-97-7)

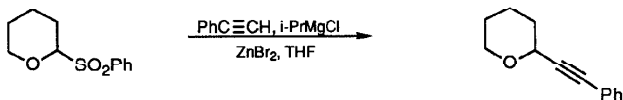
Azobisisobutyronitrile: Propionitrile, 2,2'-azobis[2-methyl- (8); Propanenitrile, 2,2'-azobis[2-methyl- (9); (78-67-1)

1,3-Dibromo-5,5-dimethylhydantoin: Hydantoin, 1,3-dibromo-5,5-dimethyl- (8); 2,4-Imidazolidinedione, 1,3-dibromo-5,5-dimethyl- (9); (77-48-5)

Di-tert-butyl dicarbonate: Formic acid, oxydi-, di-tert-butyl ester (8); Dicarbonic acid, bis(1,1-dimethylethyl) ester (9), (24424-99-5)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

**SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC
ETHERS: TETRAHYDRO-2-(PHENYLETHYNYL)-2H-PYRAN**
(2H-Pyran, tetrahydro-2-(phenylethenyl)-)



Submitted by Dearg S. Brown and Steven V. Ley.¹

Checked and modified by David J. Mathre and Ichiro Shinkai.

1. Procedure

An oven-dried, three-necked, 1-L, round-bottomed Morton flask equipped with a mechanical stirrer, gas bubbler outlet, 125-mL, pressure-equalizing addition funnel fitted with a rubber septum, and a nitrogen inlet (Note 1) is charged with 11.2 g (110 mmol) of phenylacetylene (Note 2) and 60 mL of dry tetrahydrofuran (THF) (Note 3). The addition funnel is charged with 60 mL of 2 M isopropylmagnesium chloride (Note 4) which is then added over a 5-min period (Note 5). The addition funnel is rinsed with 10 mL of dry THF and the solution is stirred at room temperature for 1 hr. The addition funnel is charged with 72 mL of 1 M anhydrous zinc bromide in THF (Note 6) which is then added to the light-grey solution over a 5-min period (Note 7). The addition funnel is rinsed with 10 mL of dry THF, and the mixture is stirred for a further 30 min at room temperature (Note 8). The addition funnel is charged with a solution of 22.6 g (100 mmol) of 2-(phenylsulfonyl)tetrahydro-2H-pyran (Note 2) dissolved in 100 mL of dry THF, which is then added over a 5-min period (Note 9). The resulting grey solution is stirred at room temperature for 18 hr and then quenched with 300 mL of 1 M

hydrochloric acid (Note 10). The mixture is transferred to a single necked, 1-L, round-bottomed flask and concentrated under reduced pressure (40°C, 100 mm) to remove the THF. The residue is transferred to a 1-L separatory funnel and extracted with 300 mL of isopropyl acetate (i-PrOAc). The extract is sequentially washed with water (150 mL), 1 M aqueous dibasic potassium phosphate (3 x 150 mL), and brine (150 mL). The extract is dried over anhydrous sodium sulfate, filtered through a sintered glass funnel, washing the residue with more i-PrOAc, and then concentrated under reduced pressure (40°C, 10 mm) to give 19.6 g of crude product as a pale yellow liquid (Note 11). This is distilled under reduced pressure to afford 18.3 g (98%) of tetrahydro-2-(phenylethynyl)-2H-pyran as a colorless liquid, bp 110-115°C (0.01 mm) (Note 12).

2. Notes

1. A constant stream of anhydrous nitrogen (dried over molecular sieves) was maintained throughout the reaction.

2. All the chemicals used in this procedure were purchased from Aldrich Chemical Company, Inc., and were used without further purification unless otherwise stated.

3. Tetrahydrofuran was dried over 3Å molecular sieves (residual water content <20 µg/mL) and purged with nitrogen prior to use.

4. Isopropylmagnesium bromide can also be used in this type of experiment.

5. The reaction is exothermic, the internal temperature rising from 20°C to 44°C. *Caution: Do not run the reaction under more concentrated conditions, or on a larger scale without providing external cooling.*

6. Zinc bromide (100 g, 440 mmol) (98+%, Note 2) was dissolved in dry THF bringing the volume to 440 mL (exothermic heat of solution). The initial water content

(1.2 mg/mL) was reduced to <50 µg/mL by drying the solution with 3Å molecular sieves (50 g) for 24 hr.

7. The reaction is exothermic, the internal temperature rising from 20°C to 34°C. See Note 5.

8. On addition of zinc bromide a fine white precipitate is sometimes formed (observed by checkers).

9. The reaction is exothermic, raising the internal temperature from 20°C to 32°C. See Note 5.

10. The quench is exothermic during addition of the first ca. 25 mL of the aqueous hydrochloric acid, the internal temperature rising from 20°C to 30°C.

11. HPLC analysis is as follows: 94.1 wt% product, 2.4 wt% phenylacetylene, remainder i-PrOAc. HPLC conditions are as follows: [4.6 x 250 mm Zorbax RX; 40:60 H₂O (0.01 M KH₂PO₄)/MeCN; 1.5 mL/min; UV 210 nm] phenylsulfonic acid (2.6 min), 2-(phenylsulfonyl)tetrahydro-2H-pyran (4.7 min, decomposes in solution), phenylacetylene (6.1 min), tetrahydro-2-(phenylethynyl)-2H-pyran (9.2 min).

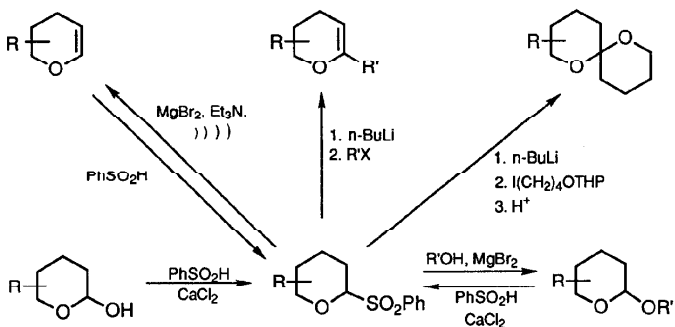
12. The physical properties are as follows: literature bp 149°C (8 mm);² HPLC analysis: >99 wt% product, <0.1% phenylacetylene; ¹H NMR (CDCl₃) δ: 1.50-2.00 (m, 6 H, C3-H₂, C4-H₂, C5-H₂), 3.53-3.66 (m, 1 H, C6-H), 4.00-4.13 (m, 1 H, C6-H), 4.52 (dd, 1 H, J = 2.8, 7.4, C2-H), 7.26-7.35 (m, 3 H, Ar-H), 7.41-7.51 (m, 2 H, Ar-H); ¹³C NMR (CDCl₃) δ: 21.8 (t), 25.7 (t), 32.2 (t), 66.6 (t), 67.5 (d), 85.2 (s), 88.1 (s), 122.8 (s), 128.2 (d), 128.3 (d), 131.8 (d).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Methods for forming carbon-carbon bonds at the anomeric position of cyclic ethers are important processes in organic synthesis. We have shown how lactols and their derivatives can be readily converted into the corresponding 2-benzenesulfonyl cyclic ethers.^{3,4} These versatile intermediates can then be transformed into the corresponding dihydropyrans,³ 2-substituted dihydropyrans,⁴ spiroacetals,^{4,5} and tetrahydropyranyl ethers⁶ (Scheme 1).

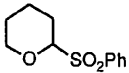
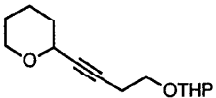
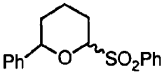
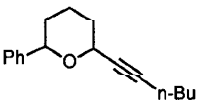
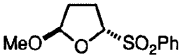
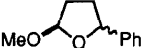
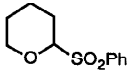
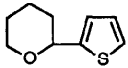
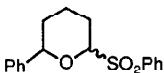
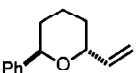
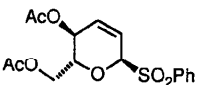
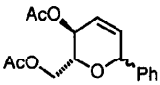


Scheme 1

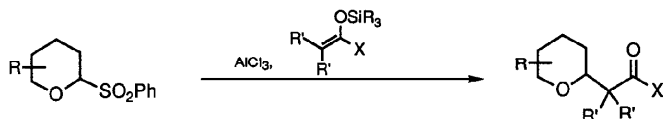
The procedure illustrated here is representative of a general and versatile method for the preparation of 2-substituted tetrahydrofurans and tetrahydropyrans from cyclic ether sulfones and the appropriate alkynyl, vinyl, or aryl Grignard reagent. From the examples shown in the Table and others previously reported,^{3,7} a selectivity for the trans-product is observed with 6-substituted tetrahydropyrans irrespective of the initial geometry of the sulfone. This implies the presence of a common reaction intermediate such as an oxonium ion which is trapped by preferred axial bond

formation at the 2-position. For 5-substituted tetrahydrofurans, significant trans-selectivity is only observed with large substituents.

TABLE
SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC ETHERS

Sulfone	Product(s)	Yield (%)
		83
		81
	 cis : trans 50 : 50	91
		95
		82
	 6R : 6S 17 : 83	54

The benzenesulfones also undergo nucleophilic displacement with silyl enol ethers and ketene silyl acetals in the presence of a Lewis acid such as aluminum trichloride (Scheme 2).⁸



Scheme 2

1. Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, SW7 2AY, UK
2. Zelinski, R.; Louvar, J. *J. Org. Chem.* **1958**, *23*, 807.
3. Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.
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5. Greck, C.; Grice, P.; Ley, S. V.; Wonnacott, A. *Tetrahedron Lett.* **1986**, *27*, 5277.
6. Brown, D. S.; Ley, S. V.; Vile, S. *Tetrahedron Lett.* **1988**, *29*, 4873.
7. Brown, D. S.; Ley, S. V. *Tetrahedron Lett.* **1988**, *29*, 4869.
8. Brown, D. S.; Ley, S. V.; Bruno, M. *Heterocycles* **1989**, *28*, 773.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tetrahydro-2-(phenylethynyl)-2H-pyran: 2H-Pyran, tetrahydro-2-(phenylethynyl)-
(10); (70141-82-1)

Phenylacetylene: Benzene, ethynyl- (8,9); (536-74-3)

Isopropylmagnesium chloride: Magnesium, chloroisopropyl- (8);

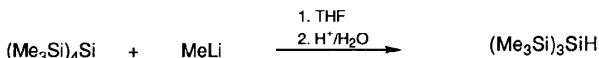
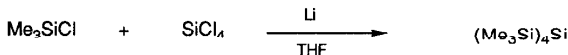
Magnesium, chloro(1-methylethyl)- (9); (1066-55-9)

Zinc bromide (8,9); (7699-45-8)

2-(Phenylsulfonyl)tetrahydro-2H-pyran: 2H-Pyran, tetrahydro-2-(phenylsulfonyl)-
(11); (96754-03-9)

TRIS(TRIMETHYLSILYL)SILANE

(Trisilane, 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)-)



Submitted by Joachim Dickhaut and Bernd Giese.¹

Checked by George A. O'Doherty and Leo A. Paquette.

1. Procedure

Lithium powder (7.55 g, 1.07 mol) is placed in a 500-mL, four-necked flask equipped with a condenser, mechanical stirrer, dropping funnel, and low-temperature thermometer (Notes 1 and 2). The apparatus is carefully flushed several times with nitrogen followed by the addition of 50 mL of anhydrous tetrahydrofuran (THF). The reaction flask is cooled to approximately -60°C in a dry ice-acetone bath, and a mixture of freshly distilled (from CaH_2) chlorotrimethylsilane (54.8 mL, 47.1 g, 0.43 mol) and tetrachlorosilane (Note 3) (10.1 mL, 15.0 g, 0.09 mol) in 140 mL of anhydrous THF is added over 1 hr by dropping funnel so that the temperature of the reaction mixture never exceeds -30°C. After addition is complete, stirring is continued for 0.5 hr with cooling (Note 4). The gold-brown suspension is allowed to warm to room temperature and stirred for 12 hr, during which time the color becomes more intense (Note 5). The thermometer is removed and the mixture is heated to reflux for 2 hr to destroy the remaining chlorotrimethylsilane. After the condenser is cooled to room

temperature, it is replaced with a nitrogen bubbler and gas inlet. Methyllithium-lithium bromide complex (66 mL, 99 mmol, 1.5 M in ether) is added over 3 hr to the grey-brown mixture with vigorous stirring (Note 6). During the addition a continuous stream of nitrogen is bubbled through the reaction mixture. After the reaction mixture is stirred for an additional 16 hr at room temperature, it acquires a greenish tint. Hydrolysis is carried out by the careful addition of the reaction mixture to 400 mL of ice-cold 2 N hydrochloric acid. [*Caution: The solid residue may be highly pyrophoric. The checkers blanketed the flask with argon prior to the introduction of ether (100 mL) and poured the vigorously stirred slurry into the cold hydrochloric acid. This rinse procedure was repeated twice more.*] The aqueous phase is extracted four times with 200-mL portions of pentane, the combined organic phases are dried over magnesium sulfate and the solvents removed under reduced pressure. Distillation under reduced pressure (1 mm, 38°C) affords 13.4-17.2 g of the product as a clear oil (60-77% yield).

2. Notes

1. The checkers used a three-necked flask having one arm equipped with a Claisen head.
2. All reagents were purchased from Fluka Chemical Corporation, except the methyllithium-lithium bromide complex, which was purchased from Aldrich Chemical Company, Inc., and were used without further purification. The lithium powder can be weighed in air; however, the use of a dust mask is recommended.
3. As tetrachlorosilane smokes strongly when exposed to air, introduction to the addition funnel is best carried out using a syringe.
4. If the temperature falls below -60°C, the mixture may solidify, but returns to a liquid upon warming.

5. The synthesis should be carried out over three days, stirring the mixture overnight. The stirring times reported should be considered a minimum, and need not be followed exactly.

6. A clean dropping funnel should be used for the addition of the methyllithium solution, and should be filled with rigorous exclusion of air. It is simpler to employ a syringe pump, and replace the dropping funnel with a septum. In this case the stream of nitrogen can be introduced by a needle through the septum.

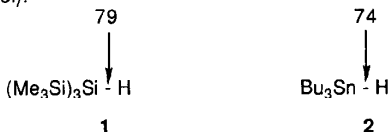
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Tris(trimethylsilyl)silane **1** can be substituted for toxic stannanes like tributylstannane **2** in organic syntheses which involve radicals,² because: a) silyl radicals are as efficient as stannyl radicals in the radical-forming step,³ and b) the Si-H bond strength in tris(trimethylsilyl)silane **1** is only slightly higher than the Sn-H bond strength in tributylstannane **2**.⁴

Bond energy (kcal/mol):



Thus, heating a mixture of an organic bromide or iodide with equimolar amounts of silane **1** and catalytic amounts of a radical initiator like azobisisobutyronitrile gives organic radicals **3** that can undergo addition, cyclization or rearrangement reactions² (**3** → **4**) before hydrogen abstraction⁵ yields the product.



Tris(trimethylsilyl)silane **1** is a mediator in this reaction. In contrast to the reported method,⁶ the synthesis described in this procedure gives silane **1** in high yields in a one-pot reaction.

1. Institute of Organic Chemistry, University of Basel, St. Johannis-Ring 19, CH-4056 Basel, Switzerland.
2. Giese, B.; Kopping, B.; Chatgililoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681; Kulicke, K. J.; Giese, B. *Synlett.* **1990**, 91.
3. Ballestri, M.; Chatgililoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678.
4. Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgililoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267.
5. Chatgililoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641.
6. Gilman, H.; Smith, C. L. *J. Organometal. Chem.* **1968**, *14*, 91; Gutekunst, G.; Brook, A. G. *J. Organometal. Chem.* **1982**, *225*, 1; Bürger, H.; Kilian, W. *J. Organomet. Chem.* **1969**, *18*, 299.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tris(trimethylsilyl)silane: Trisilane, 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)-
(8,9); (1873-77-4)

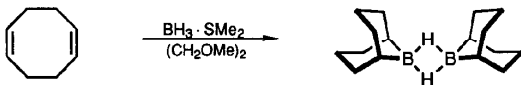
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Tetrachlorosilane: Silicon chloride (8); Silane, tetrachloro- (9); (10026-04-7)

Methylithium-lithium bromide complex: Lithium, methyl- (8,9); (917-54-4)

9-BORABICYCLO[3.3.1]NONANE DIMER

(9-Borabicyclo[3.3.1]nonane, dimer)



Submitted by John A. Soderquist¹ and Alvin Negron.

Checked by Daniel M. Berger and Larry E. Overman.

1. Procedure

Caution! The manipulation and handling of air-sensitive compounds requires the use of special techniques. While no difficulties have been encountered with the present procedures, the preparer should consult References 2 and 3 prior to carrying out these syntheses.

A 2-L, three-necked, round-bottomed flask containing a magnetic stirring bar is fitted with a 250-mL addition funnel and a distillation assembly set for downward distillation to a 500-mL receiver flask. Rubber septa are used to isolate the system from atmospheric contact. Under a nitrogen purge, vented to an exhaust hood through a mercury bubbler, the entire system is thoroughly flame-dried (Note 1). After the 2-L flask is cooled to room temperature, it is charged with 500 mL of pure, dry 1,2-dimethoxyethane (Note 2) and 153 mL (1.53 mol) of borane-methyl sulfide complex (Note 3) employing a double-ended needle to effect the transfer. With a similar technique, 164 g (1.52 mol) of 1,5-cyclooctadiene (Note 4) is transferred to the addition funnel. To the stirred borane solution, 1,5-cyclooctadiene is added dropwise over ca. 1 hr to maintain a reaction temperature of 50-60°C during which time a small

amount of dimethyl sulfide (bp 38°C) distills slowly from the reaction mixture. After the addition is completed, the addition funnel is replaced with a glass stopper and approximately 300 mL of the solution is distilled to reach a final distillation temperature of 85°C, indicating the complete removal of dimethyl sulfide from the reaction mixture (Note 5). If the distillate temperature does not reach 85°C, 150 mL of additional 1,2-dimethoxyethane is added and the distillation is continued until the distillate temperature reaches 85°C. The distillation assembly is replaced with a rubber septum and 1,2-dimethoxyethane is added to the reaction flask to bring the total liquid volume to 1 L. The mixture is warmed to effect the dissolution of the solid and allowed to cool very slowly to 0°C, which results in the formation of crystalline 9-borabicyclo[3.3.1]nonane (9-BBN) dimer. The supernatant liquid is decanted from the product using a double-ended needle and the 9-BBN dimer is dissolved in 1 L of fresh 1,2-dimethoxyethane. After the flask is cooled to 0°C, the supernatant liquid is removed as above and the large needles are dried under reduced pressure for 12 hr at 0.1 mm to give 158-165 g (85-89%) of product (mp 152-154°C, sealed capillary) (Notes 6-8).

2. Notes

1. Alternatively, the apparatus can be dried for 4 hr at 150°C, assembled hot and purged with dry nitrogen.

2. 1,2-Dimethoxyethane, available from the Aldrich Chemical Company, Inc., was predried over calcium hydride and distilled from sodium/benzophenone prior to use. The solvent was used directly after purification or stored in an ampule bottle, available from the Aldrich Chemical Company, Inc., under a nitrogen atmosphere.

3. Borane-methyl sulfide complex, obtained from the Aldrich Chemical Company, Inc., was used directly without additional purification. However, titration of

the reagent was carried out with glycerol as described² to determine its actual molarity. Older samples of this reagent can be distilled under aspirator vacuum to obtain pure reagent.

4. 1,5-Cyclooctadiene, obtained from the Aldrich Chemical Company, Inc., was distilled under aspirator pressure from lithium aluminum hydride prior to use.

5. Failure to remove the dimethyl sulfide from the reaction mixture increases the solubility of the 9-BBN dimer and lowers the overall yield to ca. 65%.

6. The spectra of the product are as follows: ¹H NMR (300 MHz, C₆D₆) δ: 1.44-1.57 (m, 4 H), 1.58-1.74 (m, 12 H), 1.83-2.07 (m, 12 H). A standard HETCOR experiment revealed that protons on each of the methylene carbons were superimposed upon one another to give rise to these downfield multiplets; ¹³C NMR (75 MHz, C₆D₆) δ: 20.2 (br, C 1,5), 24.3 (C 3,7), 33.6 (C 2,4,6,8); ¹¹B NMR (96 MHz, C₆D₆) δ: 28.

7. The 9-BBN dimer so prepared is reasonably air-stable so that exposure to the atmosphere for 1 month lowered the mp to ca. 146-151°C.

8. Purification of commercial 9-BBN and other samples can be effected by recrystallization from 1,2-dimethoxyethane. Insoluble impurities can be removed from hot 1,2-dimethoxyethane solutions of 9-BBN by decantation of the solution to a second dry flask. To prevent clogging of the double-ended needle during the transfer process it is important to keep the ends of needle below the liquid surfaces. We have found that the receiver vessel should be charged with a small quantity of fresh, hot 1,2-dimethoxyethane prior to decantation and that a portion of this material should be transferred under a positive pressure of nitrogen to the 9-BBN solution to warm initially the transfer needle. Subsequently, the hot 9-BBN solution can be transferred without difficulty.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

9-Borabicyclo[3.3.1]nonane (9-BBN) has been prepared by the thermal redistribution of 9-n-propyl-9-BBN,⁴ and the hydroboration of 1,5-cyclooctadiene with borane-tetrahydrofuran complex followed by thermal isomerization of the mixture of dialkylboranes at 65°C.⁵ Solutions of 9-BBN have been prepared from the hydroboration of 1,5-cyclooctadiene with borane-methyl sulfide in solvents other than THF.⁶ The present procedure involves the cyclic hydroboration of 1,5-cyclooctadiene with borane-methyl sulfide in 1,2-dimethoxyethane.⁷ Distillative removal of the dimethyl sulfide in this special solvent system provides a medium that gives high purity, large needles of crystalline 9-BBN dimer in excellent yield. The material can be handled in air for brief periods without measurable decomposition.

As a dialkylborane, 9-borabicyclo[3.3.1]nonane (9-BBN) is unrivaled in both stability and selectivity.⁸ It has been distilled (bp 195°C, 12 mm) and exhibits a strong characteristic IR absorption band at 1560 cm⁻¹ (B-H-B) for the bridged dimeric structure.⁵ The crystal structure of 9-BBN dimer has been determined⁹ and the drawing above approximates the conformational features of this compound. The ¹³C NMR properties of 9-BBN adducts have been studied extensively.¹⁰

Since the 9-methoxy derivative of 9-BBN is a common by-product of several reactions of 9-BBN,¹¹ its efficient conversion back to 9-BBN has been described.¹² Such a process enables one to recycle 9-BBN in reactions which require its high regioselectivity in hydroboration reactions and the related organoborane conversions.

The selective transformations of 9-DDN are numerous and varied, with derivatives being readily prepared through both hydroboration and organometallic methodology.⁸ It has been used for the preparation of isomerically-pure boracycles,^{11,13} the highly enantioselective reduction of aldehydes and ketones,¹⁴ the preparation of new selective borohydride reducing agents,¹⁵ C-C bond-forming transformations,¹⁶ and radiopharmaceutical labeling.¹⁷ Its reactivity has made it the reagent of choice for many organoborane conversions.¹⁸ The stability and distinctive spectral properties of 9-BBN have provided the initial key information to unravel the details of hydroboration reactions.^{8,19}

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Appendix

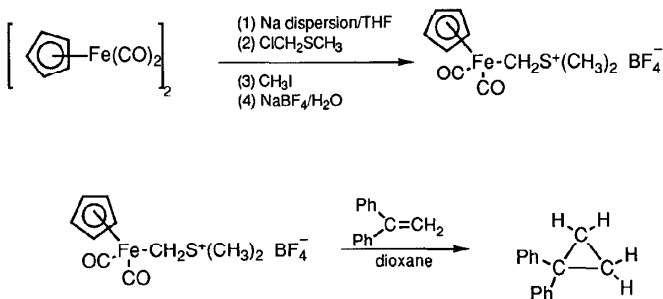
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 9-Borabicyclo[3.3.1]nonane dimer: 9-Borabicyclo[3.3.1]nonane, dimer
(10); (70658-61-6); Diborane (6), 1,1:2,2-di-1,5-cyclooctylene- [Available from Aldrich
Chemical Company, Inc.] (8,9); (21205-91-4)
- 9-Borabicyclo[3.3.1]nonane (8,9); (280-64-8)
- Dimethoxyethane: Ethane, 1,2-dimethoxy- (8,9); (110-71-4)
- Borane-methyl sulfide complex: Methyl sulfide, compd. with borane (1:1) (8);
- Borane, compd. with thiobis[methane] (1:1) (9); (13292-87-0)
- 1,5-Cyclooctadiene (8,9); (111-78-4)
- 9-Methoxy-9-borabicyclo[3.3.1]nonane: 9-Borabicyclo[3.3.1]nonane, 9-methoxy- (9);
(38050-71-4)

CYCLOPROPANATION USING AN IRON-CONTAINING METHYLENE

TRANSFER REAGENT: 1,1-DIPHENYLCYCLOPROPANE

(Iron (1+), dicarbonyl(η^5 -2,4-cyclopentadien-1-yl)(dimethylsulfonium
 η -methylide)-, tetrafluoroborate (1-))



Submitted by Matthew N. Mattson,^{1a} Edward J. O'Connor,^{1b} and Paul Helquist.^{1a}
 Checked by Jörn-Bernd Pannek and Ekkehard Winterfeldt.

1. Procedure

CAUTION! This experiment should be performed in an efficient fume hood because of the unpleasant odors of sulfide-containing materials. In addition, the first part of this procedure should be conducted behind a safety shield because of the use of highly reactive sodium metal.

Into a dry, one-necked, 2000-mL, round-bottomed flask is placed a medium-sized magnetic stirring bar (Note 1) and cyclopentadienyliron dicarbonyl dimer $[\text{C}_5\text{H}_5(\text{CO})_2\text{Fe}]_2$, (0.50 mol equiv, 0.21 mol, 74.4 g; Notes 2 and 3). Sodium dispersion (40% by weight) in light mineral oil (1.25 mol equiv, 0.52 mol, 30.1 g; Notes

4 and 5) is weighed into the flask (Note 6). The flask is then equipped with a reflux condenser topped with a three-way stopcock (Note 7) having a vertical tubulation capped with a septum through which solvents and reagents can be introduced with long needles or cannulas. By evacuation through the other tubulation of the stopcock, the apparatus is evacuated and filled with nitrogen twice, then placed under vacuum (≤ 0.1 mm) for 1 to 2 hr to remove the bulk of the mineral oil. The flask is filled with nitrogen, and tetrahydrofuran (THF; 850 mL; Note 8) is transferred into the flask. Rapid stirring is begun and maintained while an oil bath or a heating mantle is employed to heat the mixture at reflux for ≥ 18 hr.

The flask is cooled to 0°C in an ice bath, and chloromethyl methyl sulfide (1.00 mol equiv, 0.42 mol, 35.2 ml) is added dropwise with a syringe over 25 min (Notes 9 and 10). After residues of the sulfide are rinsed into the flask with additional THF (ca. 5-10 mL), the mixture is stirred at 0°C for 1 hr and then at 25°C for 1 hr (Note 11). Iodomethane (1.30 mol equiv, 0.55 mol, 34.0 mL; Note 12) is added over 5 min using a syringe. After residues of iodomethane are rinsed into the flask with THF (5-10 mL), the mixture is stirred at 25°C for ≥ 15 hr. Stirring is stopped (Note 13), and the volatile materials are removed under vacuum (≤ 0.1 mm) using a large, liquid nitrogen-cooled trap (Note 14). The vacuum in the apparatus is relieved with nitrogen, and the three-way stopcock is removed from the top of the condenser, exposing the reaction mixture to air.

In a 2000-mL Erlenmeyer flask containing a magnetic stirring bar, a solution of sodium tetrafluoroborate (6.00 mol equiv, 2.52 mol, 277 g) in water (1200 mL total volume of solution) is prepared and heated to 95°C while being stirred. A 1000-mL portion of the hot sodium tetrafluoroborate solution is slowly poured down the condenser into the reaction mixture which is kept at ca. 95°C while being stirred. At the same time, a 350-mL, medium-frit, sintered-glass Büchner funnel is prepared with a 2.5-cm layer of diatomaceous earth and a 1-cm layer of sand covered with a piece of

filter paper with holes punched in it, and the funnel is preheated by passage, with suction, of 700-1000 mL of hot, distilled water which is then discarded. The condenser is removed from the reaction flask, and the contents are suction-filtered through the hot funnel into a heated, 2000-mL filter flask (Note 15). The remaining hot sodium tetrafluoroborate solution is used to rinse the reaction flask and the hot funnel. The combined filtrates are swirled while being cooled. If necessary, a seed crystal can be added. The filtration flask is placed in an ice bath while swirling is continued. After the temperature reaches 0°C, the flask is placed in a freezer at ca. -10°C for 1-3 hr. The product is collected by suction filtration using a large, chilled Büchner funnel (Whatman no. 1 filter paper) and is rinsed with ice-cold distilled water (150 mL) and cold diethyl ether (1500 mL). The filter cake is broken up, and the crystals are dried in a stream of air overnight. There is obtained 100.6 g (70.4%) of $(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2\text{FeCH}_2\text{S}^+(\text{CH}_3)_2\text{BF}_4^-$ as free-flowing, flake-like, amber crystals (Notes 16-18). The yields were found to be considerably lower on runs of smaller scale (Note 19).

Into a 200-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar are placed the crystalline reagent (35 g, 0.10 mol; Note 20), 1,1-diphenylethene (9.1 mL, 9.3 g, 0.05 mol; Note 21), and dioxane (25 mL; Notes 22 and 23). The flask is equipped with a reflux condenser topped with a stopcock, and a nitrogen atmosphere (Note 24) is established within the apparatus. While being stirred vigorously, the heterogeneous mixture is heated to reflux in an oil bath (120°C) for 14 hr (Note 25). The brown mixture is removed from the oil bath and allowed to cool sufficiently to permit the addition of hexane (75 mL, Note 26) to the flask. The mixture is stirred in the air until the flask reaches 25°C. The supernatant liquid containing the product is poured from the flask and filtered through Whatman no. 1 filter paper. The remaining solid is repeatedly suspended and washed with several portions of hexane (ca. 1000 mL total; Note 27). The combined filtrates are filtered

through a pad of silica gel in a sintered glass Büchner funnel and are then concentrated by rotary evaporation. The residual dark brown oil is dissolved in methanol (200 mL) to give an orange-brown solution which immediately becomes dark green when solid ferric chloride (7 g; Note 28) is added at 25°C. The mixture is stirred for 15 min and then concentrated by rotary evaporation. The residual dark green oil is extracted with two 200-mL portions of hexane, and the combined extracts are filtered through a pad of silica gel and concentrated by rotary evaporation. The colorless oil that remains is distilled through a short-path apparatus to give 8.76 g (88%) of 1,1-diphenylcyclopropane as a clear, colorless liquid, bp 89°C (0.8 mm; lit⁸ 110-111°C, 1.3 mm; Note 29). The checkers obtained 65-77% yield of product on roughly half the scale.

2. Notes

1. The stirring bar must be able to stir the heterogeneous reaction mixture rapidly. Very good stirring is required for the metallic sodium dispersion to react efficiently. A medium-sized, egg-shaped stirring bar (32 x 16 mm, available from Fisher Scientific Company) was found to be particularly effective.

2. Cyclopentadienyliron dicarbonyl dimer $[\text{C}_5\text{H}_5(\text{CO})_2\text{Fe}]_2$ can be purchased from Alfa Products, Morton/Thiokol Inc. or Aldrich Chemical Company, Inc. Alternatively, it is easily and inexpensively prepared by heating dicyclopentadiene with iron pentacarbonyl. Our yield (80-90%) of this reagent is considerably higher than that reported in the literature procedure.²

3. In order to allow for proper placement of the sodium dispersion in the flask later (Note 5), the $[\text{C}_5\text{H}_5(\text{CO})_2\text{Fe}]_2$ was neatly piled in a mound on top of the stirring bar in the middle of the bottom of the flask.

4. The 40% (by weight) sodium dispersion in light mineral oil was used as obtained from Aldrich Chemical Company, Inc., except for thorough shaking immediately prior to transfer of the dispersion.

5. A 1-cm diameter glass tube narrowed to a tip at one end and equipped with a pipet bulb was used to transfer the dispersion which was carefully placed around the perimeter of the mound of $[\text{C}_5\text{H}_5(\text{CO})_2\text{Fe}]_2$. After evaporation of the oil, the stirring bar should rest in the center of the ring of sodium without contacting it. In this way, the reaction mixture can subsequently be stirred more efficiently. Also, all of the sodium should lie below the surface of the tetrahydrofuran solution formed, so that the mixture reacts efficiently upon being heated at reflux.

6. The procedure described here for reductive cleavage of this compound with sodium dispersion³ to give sodium cyclopentadienyldicarbonylferrate is considerably more convenient and less hazardous than the more traditional use of sodium amalgam that was reported previously.⁴

7. The stopcock used in this procedure is of the design shown in Figure 1. A source of inert gas and vacuum can be attached to the horizontal tubulation. The vertical tubulation is capped with a septum to allow introduction of liquid reagents and solvents through use of a long syringe needle or cannula inserted through the septum and down through the body of the stopcock. In order to avoid air leaks through the septum into the reaction apparatus when reagents are not being added, the stopcock is normally turned to close off the vertical tubulation, but to leave the flask open to the nitrogen/vacuum source.

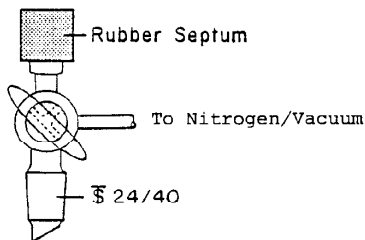


Figure 1

8. Commercial, anhydrous-grade tetrahydrofuran (THF) is further purified by distillation from a dark blue or purple solution of sodium benzophenone ketyl or dianion under nitrogen. One method for transferring the THF into the reaction flask is through the use of cannulas. The cannulas (available from Aldrich Chemical Company, Inc.) are constructed from 60-cm sections of 18-gauge stainless steel tubing with a needle tip at each end. It is perhaps more convenient to use two short sections of needle tubing (each having a needle point at only one end) joined with 25-50 cm of small-diameter Teflon tubing. Transfer through the cannula is facilitated by applying a slight vacuum to the reaction apparatus while maintaining a positive pressure of nitrogen in the flask originally containing the distilled THF. Alternatively, the THF can be distilled directly into the reaction flask.

9. Chloromethyl methyl sulfide was obtained from Aldrich Chemical Company, Inc. and distilled under nitrogen prior to use, although direct use of the commercial material without distillation had little effect on the overall efficiency of this procedure.

10. **WARNING:** Chloromethyl methyl sulfide has a very unpleasant, penetrating odor and should be handled in a properly ventilated fume hood. Also, because of its structural similarity to chloromethyl methyl ether which is highly toxic and an OSHA-regulated carcinogen, this sulfide should be handled as a substance having potentially similar toxic properties.

11. The product of this alkylation step is $(\eta^5\text{-C}_5\text{H}_5)(\text{CO})_2\text{FeCH}_2\text{SCH}_3$ which is used directly in the next step but which, if desired, can be isolated as a dark yellow-brown, somewhat air-sensitive oil in greater than 90% yield.^{5,6}

12. Iodomethane (99%) was used as obtained from Aldrich Chemical Company, Inc. Excess iodomethane is used to quench any unreacted sodium metal.

13. At this point, the flask can be swirled so that any small amounts of sodium adhering to the wall of the flask above the solution level can be coated with the reaction mixture.

14. Trapping of the unreacted chloromethyl methyl sulfide in the cold trap is recommended because of the problems summarized in Note 10.

15. In order for this filtration to proceed smoothly, the funnel and its contents must remain hot to avoid premature crystallization of the product and clogging of the funnel. Minor clogging can be remedied by addition of a 100-mL portion of boiling distilled water to the funnel. Major clogging may require addition of boiling water and agitation of the filtration media with a spatula. This addition, however, may reduce the yield of the crystallized product.

16. Physical data for this compound are the following: mp 129-130°C (corrected); IR (KBr pellet) cm^{-1} : 3120, 3035, 2040, 1955, 1417, 1328, 1280, 1055, 852; ^1H NMR (80 MHz, CD_3NO_2) δ : 2.72 (s, 2 H, CH_2), 3.00 (s, 6 H, 2 CH_3), 5.34 (s, 5 H, C_5H_5); ^{13}C NMR (20 MHz, CD_3NO_2) 13.35 (CH_2), 31.20 (CH_3), 87.88 (C_5H_5), 215.56 (CO).

17. This material is satisfactory for alkene cyclopropanation reactions, although recrystallization can be effected very easily by dissolving the crude product in nitromethane at 25°C in the air and by slowly cooling the filtered solution to -70°C. The recrystallization recovery is greater than 80% and provides large, "gem-like," amber-colored crystals. Acetone can also be used as the recrystallization solvent.

18. This reagent can be stored in ordinary flasks or bottles in the air, but it should be protected from bright light, which leads to slow decomposition. Storage in a dark brown bottle is recommended.

19. The checkers' yields ranged from 25-46% in preparations that were run on one-fourth to one-half of the scale used by the submitters.

20. A two-fold excess of the iron reagent is employed to assure high conversion of the alkene to the cyclopropane. Equimolar amounts of the starting materials can be used, but the cyclopropane yield is ca. 20% lower.

21. 1,1-Diphenylethene is obtained from Aldrich Chemical Company, Inc. and is used without further purification.

22. 1,4-Dioxane is distilled from sodium benzophenone ketyl under nitrogen.

23. Nitromethane is also a good solvent for this reaction, and in some cases gives somewhat higher yields of cyclopropanes. Also, the reaction times are reduced to 2-4 hr when nitromethane is used. Before use, this solvent is purified according to a published procedure.⁷ Commercially obtained solvent is first dried over anhydrous magnesium sulfate and then over anhydrous calcium sulfate. The solvent is filtered into a flask containing activated 3 Å molecular sieves and is heated at 60°C for 8 hr while being stirred. Nitromethane is distilled from the powdered molecular sieves under reduced pressure (bp 58°C, 150 mm; lit.⁷ 58°C, 160 mm) directly into a flask containing additional 3 Å molecular sieves. The purified solvent is stored in the dark. When "wet" nitromethane from commercial sources is used directly as the reaction solvent, the percent conversions of alkenes to cyclopropanes are reduced substantially. **CAUTION:** Distillations of nitromethane and reactions using this solvent at elevated temperature should be conducted behind a safety shield.

24. When the cyclopropanation reactions are run in the presence of air, the yields are slightly reduced.

25. Vigorous stirring is necessary for a reasonable rate of reaction. The mixture remains heterogeneous both before and after the iron reagent melts. Monitoring of the reaction by GLPC (2-m 5% OV-1 or SE-30) is recommended to assure maximum conversion before the reaction is stopped.

26. The function of the hexane (or pentane) is to promote precipitation of organometallic byproducts.

27. The solid is bright yellow after these washings and consists primarily of $[\text{C}_5\text{H}_5(\text{CO})_2\text{FeS}(\text{CH}_3)_2]^+ \text{BF}_4^-$ and some unreacted cyclopropanation reagent. The latter can be recovered if desired by recrystallization of this mixture from acetone.

28. Ferric chloride destroys ferrocene, a contaminating side product that is difficult to remove by physical means because of its hydrocarbon-like characteristics.

29. The purity of this product is greater than 98% as determined by GLPC (2-m 5% OV-1 or SE-30). The spectral properties are as follows: ^1H NMR (300 MHz, CDCl_3 , cf. lit.⁸) δ : 1.30 (s, 4 H, 2 cyclopropyl CH_2), 7.12-7.40 (m, 10 H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ : 16.33 (cyclopropyl CH_2), 29.97 (quaternary cyclopropyl C), 125.9 (para C), 128.2, 128.4 (ortho and meta C), 145.8 (ipso C); MS (EI, 70 eV) m/e (rel intensity) 194 (M^+ , 86), 193 (100), 178 (64), 115 (9).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Despite their high ring strain, cyclopropanes are commonly encountered among naturally occurring as well as synthetic compounds. Cyclopropanes are most commonly synthesized by addition of alkylidene units to alkenes.⁹ These reactions employ various types of carbenes, carbenoids, or diazo compounds. One particularly important method is the Simmons-Smith reaction^{9b} which, according to the original procedure, involves the treatment of diiodomethane with zinc-copper couple to generate a reactive intermediate that serves as a cyclopropanation reagent. Several modifications of this procedure have been reported more recently. Another common approach is to employ a dihalocarbene to give a 1,1-dihalocyclopropane which is treated subsequently with a reducing agent to effect replacement of the halide substituents by hydrogen.

In the mid-1960's, transition metal carbene complexes were first reported by E. O. Fischer.¹⁰ Although their structures may be suggestive of classical carbene-like behavior, relatively few of these complexes serve as useful cyclopropanation reagents.¹¹ Rather, these compounds exhibit their own characteristic types of reactions, many of which are useful in synthetic transformations other than cyclopropanations. Contrary to this more general case, Pettit¹² and then Green¹³ reported some early findings that indicated the possible utility of certain iron carbene complexes for three-membered ring construction. Their studies were followed by investigations of iron complexes by many others,^{9m,14} among which has been the recent work of Brookhart¹⁵ and Casey.¹⁶

Helquist has focused efforts on developing synthetically useful cyclopropanation reagents based upon the use of stable organoiron compounds which may be regarded, at least formally, as direct precursors of reactive carbene complexes. Sulfonium derivatives^{6b,17} and alkenyl complexes¹⁸ have proven to be

useful in this regard. The presently described methylene transfer reagent^{6b,17a,b} and a related ethylidene transfer reagent^{17c,d} are included among the former sulfonium salt complexes. Among the many compounds reported by Brookhart is a useful silyl ether-based reagent for ethylidene transfer^{15a} as well as a reagent for asymmetric cyclopropanations.^{15b} Helquist¹⁸ and Casey¹⁶ have also reported complexes for transfer of several more complex types of alkylidene units.

An important advantage of the presently described procedure is that the cyclopropanation reagent is unusually stable for an organometallic compound. Not only is the solid reagent stable to air indefinitely, but its crystallization is accomplished from hot aqueous solutions. Samples of this reagent have been stored in ordinary laboratory reagent bottles for more than five years with no noticeable decomposition. This stability is in contrast to typical Simmons-Smith intermediates and diazoalkanes. Another advantage of the present reagent is that once it has been prepared, its subsequent use in cyclopropanation reactions is trivially straightforward. The reagent can be handled as an ordinary laboratory reagent and combined with an alkene substrate and a suitable solvent in an ordinary flask. Although an inert atmosphere is specified for the present cyclopropanation, these reactions have also been performed routinely in the air with only small reductions in yields.

1,1-Diphenylcyclopropane has been prepared previously by (1) the Simmons-Smith procedure (24% yield)^{9b,19} and modified versions of this method (up to 72%),²⁰ (2) sulfonium ylide addition to 1,1-diphenylethene (61% yield),²¹ (3) reduction of 1,1-diphenyl-2,2-dihalocyclopropanes with sodium in ammonia (47% yield),²² with sodium and tert-butyl alcohol (80%),⁸ or with diethyl lithiomethanephosphonate (62%),²³ (4) base-promoted cyclization of trimethyl(3,3-diphenylpropyl)ammonium iodide (78%),²⁴ (5) boron trifluoride-promoted cyclization of a corresponding 3-hydroxypropylstannane (97%),²⁵ (6) reaction of 3,3-diphenylpropenoic acid with lithium aluminum hydride (62%),²⁶ (7) reaction of

diphenylmethane with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ (20%),²⁷ (8) decomposition of the pyrazoline (unspecified yield) obtained by addition of diazomethane to 1,1-diphenylethene,²⁸ (9) thermolysis of a corresponding acyldiazene (43%),²⁹ (10) photolysis of 2,2-diphenylcyclobutanone (19%),²⁹ and (11) decarboxylation of 1,1-diphenyl-2-carboxycyclopropane (unspecified yield).³⁰

The Table summarizes some of the other examples of cyclopropanations that have been performed by the presently described procedure.^{6b,17a,c,31}

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

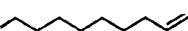





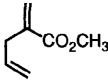
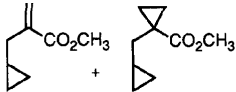
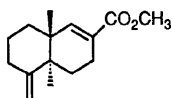
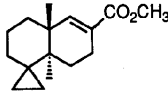
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TABLE
OTHER CYCLOPROPANATIONS USING $C_5H_5(CO)_2FeCH_2S^+(CH_3)_2 BF_4^-$

Alkene	Cyclopropane Product(s)	Consumption of Alkene (%) ^a	Yield (%) ^b
		96	92
		81	70
		100	58
		86	96
		99	62 + 5
		100	96 ^c

^aThe % consumption values were determined by quantitative GLPC measurement of unreacted alkenes using an internal standard. ^bThe yields were determined by quantitative GLPC using an internal standard and are corrected for unreacted alkenes. The reactions were typically run on 1-mmol scales. ^cTaken from ref. 31.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,1-Diphenylcyclopropane: Cyclopropane, 1,1-diphenyl- (8); Benzene, 1,1'-cyclopropylidenebis- (9); (3262-16-6)

Cyclopentadienyliron dicarbonyl dimer: Iron, tetracarbonylbis (η^5 -2,4-cyclopentadien-1-yl)di-, (Fe-Fe) (9); (38117-54-3)

Sodium (8,9); (7440-23-5)

Chloromethyl methyl sulfide: Sulfide, chloromethyl methyl (8); methane, chloro(methylthio)- (9); (2373-51-5)

Iodomethane. Methane, iodo- (8,9); (74-88-4)

Sodium tetrafluoroborate: Borate (1-), tetrafluoro-, sodium (8,9); (13755-29-8)

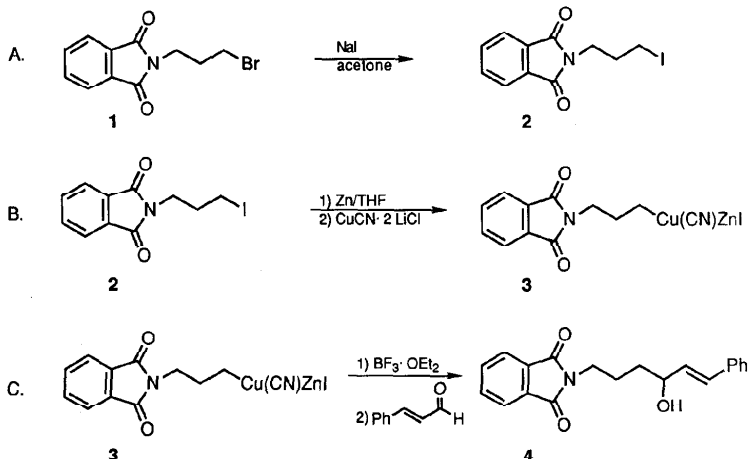
Cyclopentadienyliron dicarbonyl dimethylsulfonium tetrafluoroborate [i.e. (η^5 -C₅H₅)(CO)₂FeCH₂S⁺(CH₃)₂BF₄⁻]: Iron (1+), dicarbonyl(η^5 -2,4-cyclopentadien-1-yl)(dimethylsulfonium η -methylide)-, tetrafluoroborate (1-) (10); (72120-26-4)

1,1-Diphenylethylene: Ethylene, 1,1-diphenyl- (8); Benzene, 1,1'-ethylidenebis- (9); (530-48-3)

Dioxane: p-Dioxane (8); 1,4-Dioxane (9); (123-91-1)

Nitromethane: Methane, nitro- (8,9); (75-52-5)

**1,2-ADDITION OF A FUNCTIONALIZED ZINC-COPPER
ORGANOMETALLIC [RCu(CN)ZnI] TO AN
 α,β -UNSATURATED ALDEHYDE: (E)-2-(4-HYDROXY-6-PHENYL-5-
HEXENYL)-1H-ISOINDOLE-1,3(2H)-DIONE**
(1H-Isoindole-1,3(2H)-dione, 2-(4-hydroxy-6-phenyl-5-hexenyl)-)



Submitted by Ming Chang P. Yeh, Huai Gu Chen, and Paul Knochel.¹

Checked by Thomas Wagler, Brian F. Jones, Thomas C. Zehovitz, and David L. Coffen.

1. Procedure

A. 2-(3-Iodopropyl)-1H-isoindole-1,3(2H)-dione 2. A dry, one-necked, 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser with a gas inlet at the top, is charged with 13.4 g (50 mmol) of 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione **1** (Note 1), 17.95 g (120 mmol) of sodium iodide (Note 2), and 100 mL of acetone. The reaction mixture is stirred at reflux under nitrogen for 21 hr (Note 3). The solvent is removed on a rotary evaporator and the resulting solid is dissolved in 300 mL of dichloromethane and 200 mL of water. The two layers are separated in a separatory funnel and the aqueous layer is extracted with two 100-mL portions of dichloromethane. The combined organic extracts are washed successively with 100 mL of an aqueous 10% solution of sodium thiosulfate, three 100 mL portions of water and 150 mL of brine. The organic layer is dried over anhydrous magnesium sulfate. After filtration, the solvent is removed on a rotary evaporator. The crude white solid is dried for several hours at room temperature under reduced pressure to remove traces of solvent [15.0-15.5 g (47.6-49.2 mmol) 95-98% yield]. This material can be used directly in the next step (Note 4).

B. Formation of the copper-zinc organometallic 3 from 2-(3-iodopropyl)-1H-isoindole-1,3(2H)-dione. A dry, 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, 50-mL pressure equalizing addition funnel bearing a rubber septum, three-way stopcock, and a thermometer. The air in the flask is replaced by dry argon and the flask is charged with 4.71 g (72 mmol) of cut zinc (ca. 1.5 x 1.5 mm; Note 5). The flask is again flushed three times with argon. 1,2-Dibromoethane (Note 6), (0.2 mL, 2.3 mmol) and 3 mL of tetrahydrofuran (THF) (Note 7) are successively injected into the flask which is then heated gently with a heat gun until ebullition of solvent is observed; the zinc suspension is stirred a few minutes and heated again. The process is repeated three times; 0.15 mL (1.2 mmol) of

chlorotrimethylsilane² is then injected into the addition funnel. The cut zinc foil turns grey. After 15 min the reaction mixture is heated to 30°C with an oil bath and 18.9 g (60 mmol) of iodide **2** dissolved in 30 mL of THF is added dropwise over 40 min. After addition, the reaction mixture is stirred for 4 hr at 43°C to give a dark brown-yellow solution of the zinc reagent (Note 8). A second, dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, three-way stopcock connected to vacuum and an argon source, and two glass stoppers. The flask is charged with 4.59 g (108 mmol) of lithium chloride (Note 9). The flask is heated with an oil bath at 130°C (oil bath temperature) under vacuum (0.1 mm) for 2 hr to dry the lithium chloride. The reaction flask is then cooled to 25°C and flushed with argon. The two glass stoppers are replaced by a low temperature thermometer and a rubber septum and 4.84 g (54 mmol) of copper cyanide (Note 10) is added. The flask is flushed three times with argon and 40 mL of freshly-distilled THF (Note 7) is added to give, after 15 min, a clear yellow-green solution of the complex CuCN·2LiCl (Note 11). This solution is cooled to ca. -40°C and the two flasks are connected via a stainless steel cannula. The solution of the zinc reagent is transferred to the THF solution of copper cyanide and lithium chloride (Note 12). The resulting dark green solution is warmed to 0°C within 5 min and is ready to use in the next step after 5 min of stirring at this temperature.

C. *(E)*-2-(4-Hydroxy-6-phenyl-5-hexenyl)-1*H*-isoindole-1,3(2*H*)-dione **4**. The THF solution of the copper-zinc reagent is cooled to -78°C and 19.9 mL (162 mmol) of boron trifluoride etherate (Note 13) is added dropwise. The reaction mixture is warmed to -30°C and stirred for 30 min, then cooled to -60°C. *(E)*-Cinnamaldehyde (5.71 g, 43.2 mmol) is added slowly via a syringe. The reaction mixture is allowed to stir at -30°C for 14 hr (Note 14) and for 30 min at 0°C. After this time, conversion is complete as indicated by GLC analysis and the reaction mixture is poured into an Erlenmeyer flask containing 500 mL of ethyl acetate, 100 mL of a saturated aqueous

solution of ammonium chloride and 5 mL of ammonium hydroxide. The mixture is filtered by suction through 10 g of Celite on a sintered glass funnel, the contents of the funnel are washed twice with 50 mL of ethyl acetate and the filtrate is separated into two layers. The organic layer is washed successively with 100 mL of aqueous 10% sodium thiosulfate, and twice with 100 mL of a saturated aqueous solution of ammonium chloride. The combined aqueous phases are extracted with 100 mL of ethyl acetate and the combined organic phases are washed with 100 mL of a saturated aqueous sodium chloride solution, then dried over magnesium sulfate. After filtration, the solvent is removed on a rotary evaporator (ca. 10 mm) to afford 19.85 g of a crude yellowish oil. Flash chromatography separation⁴ of the oil using silica gel (230-400 mesh, 570 g) and ethyl acetate/hexane (1:2) gives 6.92 g (50% yield) of the 1,2-addition product **4** as a pale yellow solid, mp 87-88°C, after removal of the solvents (Note 15).

2. Notes

1. The N-(3-bromopropyl)phthalimide **1** was purchased from Aldrich Chemical Company, Inc. or from Lancaster Synthesis Ltd.

2. Sodium iodide (Analytical Reagent) was purchased from Mallinckrodt, Inc.

3. A GLC analysis (Megabore Column (DB5)) shows a conversion of 95%. The remaining bromide **1** is converted to the iodide **2** during the formation of the zinc organometallic (next reaction step).

4. The iodide **2** can be recrystallized from hexane/dichloromethane to give white needles; mp 87-88°C.³ The spectra are as follows: IR (CH_2Cl_2) cm^{-1} : 3054.6 (m), 2892.5 (w), 1773.8 (m), 1716.1 (s), 1435.8 (s), 1396.3 (m), 1265.6 (s); ^1H NMR (CDCl_3 , 360 MHz) δ : 2.25 (m, 2 H), 3.16 (t, 2 H, $J = 7.2$), 3.78 (t, 2 H, $J = 3.6$), 7.34 (dd,

2 H, $J = 6.0$ and 3.1); 7.86 (dd, 2 H, $J = 6.0$ and 3.1); ^{13}C NMR (CDCl_3 , 90.5 MHz) δ : 2.1, 32.6, 38.2, 132.7, 134.8, 168.4.

5. This procedure uses cut zinc foil purchased from Alfa Products, Morton/Thiokol Inc. (foil, 0.25 mm thick, 30 cm wide, 99.9% purity). However, zinc dust can also be used. The reaction time using zinc dust is shorter and a lower reaction temperature may be possible. After formation of the zinc organometallic, the zinc dust is allowed to settle and the THF solution of the zinc organometallic is transferred via a syringe to the THF-solution of the complex $\text{CuCN}\cdot 2\text{LiCl}$. The checkers obtained a 51-56% yield of product, melting at 80-90°C.

6. 1,2-Dibromoethane and the chlorotrimethylsilane are purchased from Aldrich Chemical Company, Inc.

7. All the tetrahydrofuran used in this procedure was freshly distilled over sodium/benzophenone before use.

8. A GLC analysis of hydrolyzed aliquots allows one to check the completion of the reaction. Less than 7% of the starting iodide 2 and more than 93% of *N*-propylphthalimide can be detected. A yield of 90% of the zinc reagent is assumed. The zinc reagent has also been formed at a reaction temperature of 33°C. A reaction time of 16 hr is then required.

9. Anhydrous lithium chloride is purchased from Aldrich Chemical Company, Inc.

10. Copper cyanide, purchased from Aldrich Chemical Company, Inc., is not a hygroscopic salt and does not need to be dried before use.

11. A very small amount of undissolved lithium chloride may still be present and will dissolve after the addition of the zinc reagent.

12. To effect the transfer, the argon pressure in the flask containing the copper salt is reduced by inserting a needle through the septum and by shutting off the argon

gas entry. Washing the remaining zinc foil with 5 mL of dry THF allows one to transfer the zinc reagent almost quantitatively.

13. Boron trifluoride etherate is purchased from Aldrich Chemical Company, Inc., and is manipulated under argon.

14. An immersion cooler (Cryocool/Neslab) is used to maintain the temperature at -30°C.

15. A portion of this product is crystallized from 1:1 ethyl acetate:hexane to yield analytically pure product, mp 92-93°C (Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.52; H, 6.03; N, 4.29). The spectra are as follows: 1H NMR ($CDCl_3$, 300 MHz) δ : 1.67-1.81 (m, 4 H), 3.75 (t, 2 H, $J = 6.9$), 4.34 (m, 1 H), 6.19 (dd, 1 H, $J = 15.9$ and 6.8), 6.56 (d, 1 H, $J = 15.9$), 7.22-7.36 (m, 5 H), 7.70 (m, 2 H), 7.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ : 24.6, 34.1, 37.7, 72.4, 123.1, 120.4, 127.0, 120.4, 128.5, 130.5, 131.9, 132.0, 133.8, 168.3; IR (CH_2Cl_2) cm^{-1} : 3489.5 (br), 3058.2 (m), 3024.8 (m), 2942.8 (m), 1771.3 (s), 1709.9 (s), 1467.6 (m), 1438.8 (s), 1398.8 (s), 1337.1 (s), 1266.2 (s), 1069.3 (m), 969.0 (m). Mass spectra (E.I.) m/e 321 (M^+ , 45), 304 (5), 263 (2), 216 (24), 189 (20), 174 (87), 160 (89), 156 (25), 148 (33), 133 (100), 115 (30), 105 (41), 91 (44), 77 (45); High resolution M.S. Anal. Calcd for $C_{20}H_{19}NO_3$: 321.1365. Found: 321.1369.

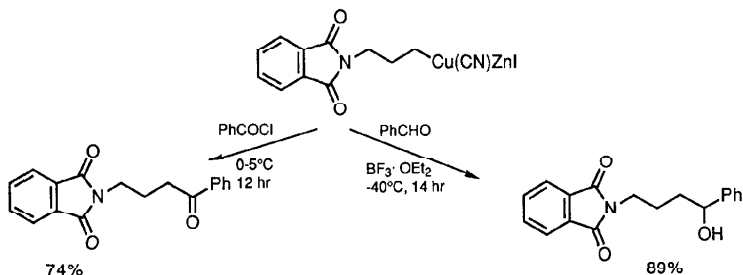
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Organometallic compounds are among the most versatile intermediates for the formation of carbon-carbon bonds, but their high reactivity allows preparation of only relatively unfunctionalized reagents. In contrast, organozinc halides with a less reactive carbon-metal bond, display a high functional group tolerance, and can include a variety of functional groups such as esters,^{5,6} enoates,^{5b,7} ketones,^{5a,8,9} nitriles,¹⁰ halides,¹¹ amino groups,^{7,12} phosphonates,¹³ thioethers,¹⁴ sulfoxides,¹⁴ and sulfones.¹⁴ A transmetalation of these zinc organometallics to the corresponding copper compounds, carried out using the THF-soluble copper salt $\text{CuCN} \cdot 2 \text{LiCl}$, affords highly reactive copper reagents $[\text{RCu}(\text{CN})\text{ZnX}]$. In this procedure, we describe the synthesis of an alkylzinc iodide with a phthalimido group at the γ -position, its conversion to the corresponding copper derivative, and its regiospecific 1,2-addition to cinnamaldehyde in the presence of boron trifluoride etherate. Copper reagent **3** reacts with several other electrophiles in excellent yields (see Scheme). This preparation illustrates the convenient synthesis of highly functionalized organozinc halides in THF¹⁵ and their high synthetic potential.

Scheme



1. The Willard H. Dow Laboratories, Department of Chemistry, The University of Michigan, Ann Arbor, MI 48109.
2. For various activations of zinc metal see: Erdik, E. *Tetrahedron* **1987**, *43*, 2203; for zinc activation with chlorotrimethylsilane, see: (a) Gawronski, J. K. *Tetrahedron Lett.* **1984**, *25*, 2605; (b) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796; (c) Picotin, G.; Miginiac, P. *Tetrahedron Lett.* **1987**, *28*, 4551.
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6. (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5559; (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z.-i. *Tetrahedron Lett.* **1986**, *27*, 955; (c) Nakamura, E.; Sekiya, K.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 337; (d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z.-i. *Org. Synth.* **1989**, *67*, 98.
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8. Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.
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10. (a) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395; (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799; (c) Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z.-i. *Angew. Chem.* **1989**, *101*, 358; *Angew. Chem., Intern. Ed. Engl.* **1989**, *28*, 351; (d) Majid, T. N.; Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069.
11. (a) Comins, D. L.; O'Connor, S. *Tetrahedron Lett.* **1987**, *28*, 1843; (b) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1986**, *29*, 6711.

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15. Gaudemar, M. *Bull. Soc. Chim. France* **1962**, 974.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(E)-2-(4-Hydroxy-6-phenyl-5-hexenyl)-1H-isoindole-1,3(2H)-dione: 1H-Isoindole-1,3(2H)-dione, 2-(4-hydroxy-6-phenyl-5-hexenyl)- (12); (121883-31-6)

2-(3-Iodopropyl)-1H-isoindole-1,3(2H)-dione: 1H-Isoindole-1,3(2H)-dione, 2-(3-iodopropyl)- (9); (5457-29-4)

2-(3-Bromopropyl)-1H-isoindole-1,3(2H)-dione: Phthalimide, N-(3-bromopropyl)- (8); 1H-Isoindole-1,3(2H)-dione, 2-(3-bromopropyl)- (9); (5460-29-7)

Sodium iodide (8,9); (7681-82-5)

Zinc (8,9); (7440-66-6)

1,2-Dibromoethane: Ethane, 1,2-dibromo- (8,9); (106-93-4)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Lithium chloride (8,9); (7447-41-8)

Copper cyanide (8,9); (544-92-3)

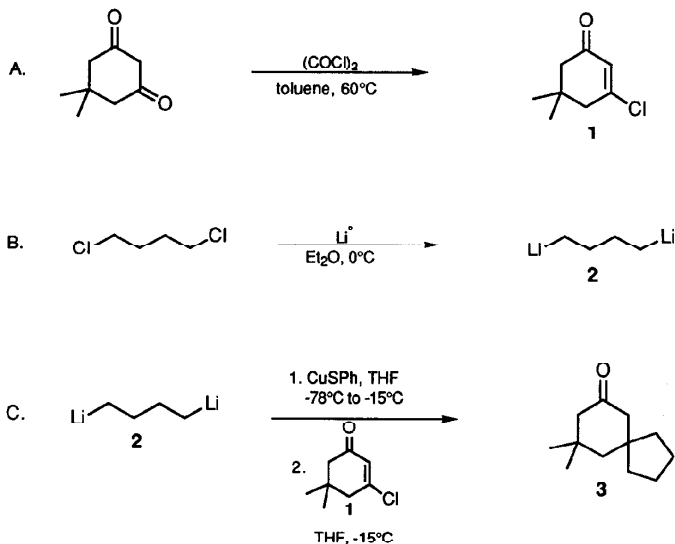
Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃) (1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

(E)-Cinnamaldehyde: Cinnamaldehyde, (E)- (8); 2-Propenal, 3-phenyl-, (E)- (9); (14371-10-9)

SPIROANNEALATION VIA ORGANOBIS(CUPRATES):

9,9-DIMETHYLSPIRO[4.5]DECAN-7-ONE

(Spiro[4.5]decan-7-one, 9,9-dimethyl-)



Submitted by Paul A. Wender,^{1,2} Alan W. White,¹ and Frank E. McDonald.²

Checked by Naoki Hirayama and Hisashi Yamamoto.

1. Procedure

Note. All reactions should be conducted in an efficient fume hood.

A. 3-Chloro-5,5-dimethylcyclohex-2-en-1-one (**1**)³ (Note 1). An oven-dried, 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and graduated addition funnel topped with a nitrogen inlet. The flask is charged with dimedone (28.1 g, 200 mmol) and toluene (100 mL) (Note 2). The suspension is stirred while oxalyl chloride (35 mL, 400 mmol) is slowly added via the addition funnel over a 10-min period (Note 3). After the addition is complete and gas evolution has subsided, the addition funnel is quickly exchanged for a reflux condenser topped with a nitrogen inlet. The mixture is then heated at 60-70°C for 30 min, or until no more suspended dimedone remains and gas evolution has ceased. (Additional oxalyl chloride may be added until dimedone has completely reacted.) The reaction is allowed to cool and concentrated by rotary evaporation at reduced pressure. The crude red oil is distilled through a short path apparatus to give 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) (29.3 g, 93% yield) as a colorless oil, bp 68-71°C (6.0 mm) (Note 4).

B. 1,4-Dilithiobutane (**2**).^{4a,5} (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a cannula or syringe.) An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar and glass beads (ca. 3-mm diameter), graduated addition funnel, stopper, and large diameter nitrogen inlet (at least 2 mm in diameter). The flask is purged with nitrogen, charged with anhydrous diethyl ether (250 mL) (Note 2), and cooled to 0°C. The stopper is removed from the flask and replaced with a conical funnel while a rapid flow of dry nitrogen is passed through the flask. Lithium wire, 1% Na (9.48 g, 1.36 mol, 4.5 eq.) (Note 5), prewashed with hexanes, is held with forceps over the funnel and cut with clean scissors into pieces no larger than 2 mm in length

(Note 6) so that the freshly cut lithium pieces drop directly into the anhydrous ether. 1,4-Dichlorobutane (33.5 mL, 300 mmol) (Note 2) is then dissolved in anhydrous diethyl ether (85 mL) and introduced into the addition funnel; approximately 10% of this solution is introduced into the lithium/ether suspension, and the reaction is initiated by vigorous stirring. A white precipitate (LiCl) signaling initiation of the reaction should be apparent within 5 to 15 min, at which time the remainder of the solution is added dropwise over a 1 to 2-hr period (Note 7). The white suspension is rapidly stirred for 20 hr at 0°C.

The mixture is most conveniently filtered by gravity filtration through an oven-dried coarse (15 μ M) sintered glass frit (Notes 8, 9). The concentration of 1,4-dilithiobutane (2) in ether is determined by titration with sec-butyl alcohol using 1,10-phenanthroline as indicator. The molarity of the solution obtained under these optimized conditions is approximately 1.7 M in "RLi", i.e., 0.9 M in 1,4-dilithiobutane (2) (Note 10). This solution is stable for several months when stored at -10°C under nitrogen.

C. *9,9-Dimethylspiro[4.5]decan-7-one* (3).⁵ (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a cannula or syringe.) An oven-dried, 2-L, three-necked, round-bottomed flask is equipped with a graduated addition funnel, overhead mechanical stirrer, and a nitrogen inlet. The flask is purged with nitrogen and charged with copper(I) thiophenoxide (36.7 g, 212 mmol) and anhydrous tetrahydrofuran (400 mL) (Note 2), and the heterogeneous suspension is mechanically stirred while cooling in a -78°C cold bath (dry ice-acetone). 1,4-Dilithiobutane (2), 0.87 (\pm 0.02) M in diethyl ether (122 mL, 106 mmol) is added via the addition funnel over 5 min, and then the reaction mixture is allowed to slowly warm to -15°C (Note 11) over a 20 to 45-min period, during which time the initial yellow color changes to brown-red with concomitant dissolution of copper thiophenoxide. The addition funnel is washed with a few

milliliters of anhydrous tetrahydrofuran, and a solution of 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) (15.85 g, 100 mmol) in anhydrous tetrahydrofuran (250 mL) is added dropwise over a 1 to 2-hr period, while the temperature of the cold bath is maintained at -15°C to -20°C. The reaction turns olive-green and then black as the chloroenone is added. After the addition is complete, the cold bath is removed and the reaction flask is allowed to warm to room temperature.

After 30 to 45 min, the reaction mixture is opened to the air and poured into approximately 500 mL of saturated aqueous ammonium chloride solution, diluted with approximately 500 mL of diethyl ether washings, and allowed to stir for 10 to 15 min. The resulting mixture is filtered through a Büchner funnel, washing with small portions of diethyl ether (Note 12). The layers are separated in a separatory funnel, the aqueous layer is extracted with diethyl ether, and the combined organic layers are washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over approximately 100 g of sodium sulfate, filtered through a Büchner funnel, and concentrated by rotary evaporation. The concentrated product may still contain solid diphenyl disulfide that can now be efficiently removed by chromatography of the neat crude product mixture through a 5-cm diameter x 10-cm height silica gel column and elution with hexane-diethyl ether (7:1) (Note 13). Evaporation of solvent by rotary evaporation at reduced pressure gives 13.28 g (74% yield) of 9,9-dimethylspiro[4.5]decan-7-one (**3**) as a pale yellow to colorless oil (Note 14).

2. Notes

1. This procedure is identical to that originally published by Heathcock and Clark,³ except that toluene has been substituted for benzene and chloroform as the solvent, because of the relative health hazards associated with the latter two solvents.

2. Dimedone, oxalyl chloride, 1,4-dichlorobutane, and copper thiophenoxide were purchased from Fluka Chemical Corporation, and were used without further purification. The checkers purchased dimedone, oxalyl chloride and 1,4-dichlorobutane from Nacalai Tesque, Inc., Kyoto, Japan and Tokyo Kasei Kogyo Co., LTD, Japan, and prepared copper thiophenoxide from thiophenol and copper(I) oxide. Toluene, diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl immediately prior to use.

3. The addition of oxalyl chloride was accompanied by much gas evolution, but no apparent exothermic reaction. Two equivalents of oxalyl chloride were required in order to consume completely the dimedone.³

4. The spectral properties of **1** were as follows: ¹H NMR (400 MHz, CDCl₃) δ: 1.10 (s, 6 H), 2.26 (s, 2 H), 2.57 (d, 2 H, J = 1.4), 6.23 (t, 1 H, J = 1.4); IR (film) cm⁻¹: 2980 (m), 1680 (s), 1616 (m), 1346 (m), 1300 (m), 1276 (m), 1008 (m). The submitters obtained 30.1 g (95% yield) of **1**, bp 79-80°C (7.5 mm).

5. Lithium wire was obtained from Aldrich Chemical Company, Inc. The use of 4.5 equiv of lithium represented a 12.5% excess. The use of only 4 equiv of lithium gave a lower titer of 1,4-dilithiobutane (**2**), and a small amount of unreacted lithium always remained even after prolonged reaction times.

6. The lithium wire must be freshly cut and in pieces not exceeding 2 mm in length. The yield dropped sharply when the average length of lithium wire was increased to 5 mm. The preparation of 1,4-dilithiobutane (**2**) from 1,4-dichlorobutane failed with the use of lithium shot^{4a} or low-sodium (<0.8% Na) lithium wire.

7. We have not yet observed an exothermic reaction in the initiation of this reaction, although maintaining the temperature at 0°C might help to control safely the lithiation reaction as well as to maximize the yield of 1,4-dilithiobutane (2).

8. Gravity filtration was preferred over vacuum filtration, since the latter method tended to pull LiCl through the frit. Small amounts of LiCl did not interfere with the formation or reaction of the biscuprate generated in Section C. The checkers used this solution without filtration.

9. In order to quench the small amount of unreacted lithium wire remaining in the reaction flask, the stopper was replaced by a reflux condenser open to the atmosphere at the top. Approximately 100 mL of diethyl ether was added to the reaction flask containing the lithium and the flask was cooled to 0°C under a stream of nitrogen. A 4:1 mixture of t-butyl alcohol : water was then added dropwise via the addition funnel until all of the lithium wire was consumed. *Caution: The quench is exothermic and is accompanied by the evolution of large amounts of hydrogen gas.* The mixture was then transferred to a separatory funnel for separation of the organic and aqueous layers followed by disposal.

10. Significant amounts of ether solvent are lost presumably by evaporation during the nitrogen flush and/or filtration steps. Thus, the molarity of the 1,4-dilithiobutane (2) solution is not an accurate indication of yield. The submitters titrated with menthol instead of with sec-butyl alcohol

11. Temperature control of the cold bath at -15°C was accomplished by addition of small amounts of dry ice to acetone and monitoring with a low-temperature thermometer. A slurry of dry ice in ethylene glycol was occasionally used as a -15°C cold bath.

12. The omnipresent solid contaminant was diphenyl disulfide, which was sparingly soluble in diethyl ether. Each filtration noted in the text was necessary for a successful workup on this large scale. The submitters used a medium (90 μ m) sintered glass frit for these filtrations. The attempted removal of product **3** by distillation from diphenyl disulfide was largely unsuccessful because of efficient entrainment of **3** in diphenyl disulfide.

13. Pure **3** is best obtained by chromatography. Product **3** could also be purified by vacuum distillation through a 10-cm Vigreux column, bp 100-103°C (2.2 mm). However, distillation did not efficiently separate **3** from diphenyl disulfide, and bumping was often a serious problem.

14. The spectral properties of **3** were as follows: ^1H NMR (400 MHz, CDCl_3) δ : 1.02 (s, 6 H), 1.42-1.68 (m, 8 H), 1.70 (s, 2 H), 2.18 (s, 2 H); IR (film) cm^{-1} : 2950 (s), 1710 (s), 1450 (m), 1370 (m), 1280 (m), 1230 (m). The submitters obtained 13.01 g (72% yield) of **3**.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

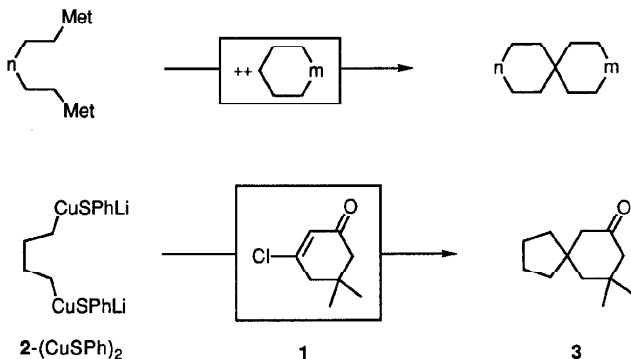
3. Discussion

The procedure in Section C is representative of the synthesis of spirobicyclic systems featuring the reaction of bis(nucleophile) reagents with geminal bis(electrophile) acceptors. This strategy provides for formation of both carbon-carbon bonds of the new ring in a single step.

The starting material 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) is easily synthesized from dimedone by the general methodology developed by Clark and Heathcock.³ The β -chlorine can also be replaced with a variety of carbon- and heteronucleophiles,⁶ and β -chloroenones can be easily reduced by zinc/silver couple to the corresponding enone.^{3b}

The formation of 1,4-dilithiobutane (**2**) was first described by West and Rochow.^{4c} The original procedure was modified by Whitesides, et al., in their pioneering studies on the synthesis and reactivity of metallocyclopentanes.^{4a-b} The methodology described in Section B is general for the synthesis of a variety of 1,4- and 1,5-dilithioalkanes, as evident in the Table below.⁵

The synthesis of 9,9-dimethylspiro[4.5]decan-7-one (**3**) uses the organobis(cuprate) derived from 1,4-dilithiobutane (**2**) as a bis(nucleophile) component, which is added to the bis(electrophile) 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**).














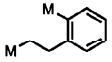

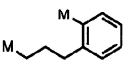

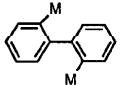

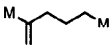

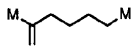



This methodology provides for spiroannulation at a carbon beta to the ketone, and is a complementary protocol for the cyclization of α,ω -dihaloalkanes to the kinetic enolates of 1,3-cycloalkanedione enol ethers (at the alpha position).⁴

The methodology has been successfully extended with modifications to both the bis(nucleophile) and the bis(electrophile) components, as shown in the Table.⁵

1. Department of Chemistry, Harvard University, Cambridge, MA 02138.
2. Department of Chemistry, Stanford University, Stanford, CA 94305.
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TABLE I
SPIROANNEALATION USING ORGANOBI(S(CUPRATES))

Reagent M = CuSPh	Equiv.	Substrate	Product	Time hr	Yield %
	1.1	1	3	1	(96)
4	1.1			1	(85)
4	1.1			1	(80)
4	1.1			18	(93)
4	1.1			1	(87)
4	1.1			1	(76)
	4.0	5		1	(74)
	1.2	5		1	(49)
	3.0	5		2	88
	3.0 10.0	5		2 2	39 94
	1.1	5		0.5	(66)
	4.0	5		0.5	(56)

Yields in parentheses were determined by internal standard gas chromatographic analysis.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

9,9-Dimethylspiro[4.5]decan-7-one: Sprio[4.5]decan-7-one, 9,9-dimethyl- (10); (63858-64-0)

3-Chloro-5,5-dimethylcyclohex-2-en-1-one: 2-Cyclohexen-1-one, 3-chloro-5,5-dimethyl- (8,9); (17530-69-7)

Dimedone: 1,3-Cyclohexanedione, 5,5-dimethyl- (8,9); (126 81 8)

Oxalyl chloride (8); Ethanedioyl dichloride (9); (79-37-8)

1,4-Dilithiobutane: Lithium, μ -tetramethylenedi- (8); μ -1,4-butanediyl-di- (9); (2123-72-0)

Lithium (8,9); (7439-93-2)

1,4-Dichlorobutane: Butane, 1,4-dichloro- (8,9); (110-56-5)

sec-Butyl alcohol: 2-Butanol, (\pm)- (8,9); (15892-23-6)

1,10-Phenanthroline (8,9); (66-71-7)

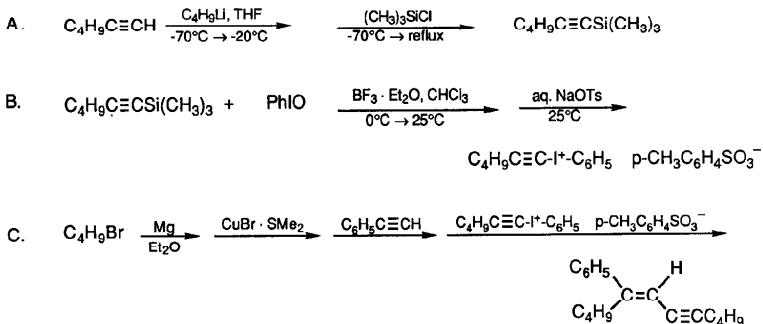
Copper(1) thiophenoxide: Benzenethiol, copper(1+) salt (8,9); (1192-40-1)

**ALKYNYL(PHENYL)IODONIUM TOSYLATES: PREPARATION AND
STEREOSPECIFIC COUPLING WITH VINYL COPPER REAGENTS.**

FORMATION OF CONJUGATED ENYNES.

**1-HEXYNYL(PHENYL)IODONIUM TOSYLATE AND
(E)-5-PHENYLDODEC-5-EN-7-YNE**

**(Iodine, 1-hexynyl(4-methylbenzenesulfonato-O)phenyl-) and
(Benzene, (1-butyl-1-octen-3-ynyl)-, (E)-)**



Submitted by Peter J. Stang and Tsugio Kitamura.¹

Checked by Kazuaki Ishihara and Hisashi Yamamoto.

1. Procedure

A. *1-Trimethylsilyl-1-hexyne* (Note 1). A dry, 500-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with one 50-mL and one 125-mL pressure-equalizing addition funnel and a reflux condenser. The top of

the condenser is mounted with a T-piece connected at one end to an argon outlet and at the other end to an oil bubbler. The apparatus is purged with dry argon and the reaction is carried out under an argon atmosphere. The flask is charged with 16.4 g (0.20 mol) of 1-hexyne (Note 2) and 200 mL of tetrahydrofuran (THF, Note 3), and the mixture is cooled to approximately -70°C with a dry ice-2-propanol slush bath. The 125-mL dropping funnel is filled with 80 mL (0.20 mol) of 1.63 M butyllithium in hexane (Note 4) which is added over a period of 30 min to the stirred, cold (-70°C) 1-hexyne in THF. After addition is complete the flask is gradually warmed over a 3-hr period to -20°C , then recooled to -70°C with the dry ice-2-propanol slush bath. Chlorotrimethylsilane (Note 5), 25.3 mL (0.20 mol), is placed in the 50-mL dropping funnel and added over a period of 15 min to the stirred, cooled reaction mixture. After the addition is complete the slush bath is removed and the mixture is first stirred at room temperature for 16 hr, then heated under reflux for 1 hr (Note 6). The mixture is cooled to 0°C with an ice-water bath and then 50 mL of water is carefully added. The entire reaction mixture is transferred to a 1-L separatory funnel and extracted with 200 mL of pentane. The organic phase is separated, washed successively with three 100-mL portions of water followed by 100 mL of saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. After filtration the solvent is distilled off through a 15-cm Vigreux column. The pale yellow residue is transferred to a 100-mL round-bottomed flask and distilled through a 15-cm Vigreux column to give 25.0-27.5 g (81-89%) of 1-trimethylsilyl-1-hexyne as a clear, colorless liquid, bp $149-156^{\circ}\text{C}$, that can be used as is in the subsequent step.

B. 1-Hexynyl(phenyl)iodonium tosylate. The center neck of a dry, 500-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with a 50-mL pressure-equalizing addition funnel. One side neck is fitted with a glass stopper and the other with a gas inlet to which is attached a T-piece connected to an argon supply and an oil bubbler. After the flask is purged with dry argon, it is charged

with 22.0 g (0.10 mol) of finely ground indosobenzene (Note 7), 200 mL of chloroform (Note 8) and 17.0 g (0.11 mol) of 1-trimethylsilyl-1-hexyne, and the entire mixture is cooled to 0°C with an ice-water bath. Boron trifluoride etherate (Note 9), 13.0 mL (0.11 mol), is added dropwise over a period of about 5 min to the stirred, cooled reaction mixture (Note 10). After the addition is complete the mixture is stirred at room temperature for about 16 hr (Note 11).

To a 1-L beaker are added 76.1 g (0.4 mol) of p-toluenesulfonic acid monohydrate (Note 12) and 400 mL of water. To this solution is carefully added 21.2 g (0.2 mol) of anhydrous sodium carbonate and then the entire solution is purged with argon for about 15 min to replace all air. This solution of sodium toluenesulfonate (NaOTs), along with the contents of the reaction flask, are placed in a 1-L separatory funnel and the mixture is vigorously shaken for a period of about 10 min (Note 13). The organic phase is separated and the aqueous phase is extracted with 50 mL of methylene chloride. The combined organic phases are dried over anhydrous magnesium sulfate, filtered and the solvent evaporated on a rotary evaporator. To the residual yellow-brown oil is added a mixture of 75 mL of diethyl ether and 75 mL of pentane resulting, after stirring, in fine white crystals. The powdery white crystals are filtered, washed with two 50-mL portions of a diethyl ether/pentane (1:1 v/v) mixture, air dried, then dried under reduced pressure. The resulting white crystalline solid, 27-34 g (60-75%), mp 77-80°C, (dec) is essentially pure and ready for most uses (Note 14).

C. (E)-5-Phenyldodec-5-en-7-yne. Caution: Dimethyl sulfide is a volatile, very smelly irritant. This reaction must be conducted in a hood!

A dry, 100-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with a 25-cm Liebig condenser, a 25-mL pressure-equalizing dropping funnel topped off with a gas-inlet, and a glass stopper. After the flask is purged with argon, it is charged with 0.90 g (37.5 mmol) of magnesium turnings and 15 mL of anhydrous ether. To the dropping funnel is added a solution of 4.0 mL (37.5

mmol) of 1-bromobutane (Note 15) in 20 mL of anhydrous ether. This solution is added to the reaction flask at such a rate (approximately 1 hr) that after the Grignard reaction is initiated a gentle reflux is maintained. After the addition is complete the mixture is stirred for an additional 30 min.

The center neck of a dry, 250-mL, three-necked, round-bottomed flask (equipped with a magnetic stirrer system) is fitted with a 50-mL pressure-equalizing dropping funnel topped off with a rubber septum and an argon inlet. The side necks are fitted with a glass stopper and a rubber septum, respectively. The apparatus is purged with argon and to the flask are added 7.7 g (37.5 mmol) of copper(I) bromide-dimethyl sulfide complex (Note 16), 60 mL of anhydrous ether, and 38 mL of dimethyl sulfide (Note 17). The mixture is cooled to -70°C with a dry ice-2-propanol slush bath. The previously prepared butyl Grignard reagent is transferred to the addition funnel via a double-ended needle with a positive argon pressure. The Grignard reagent is added dropwise, over a 30-min period, to the cooled reaction mixture (Note 18). After the addition is complete the reaction is maintained between -40°C to -50°C for 2 hr, then recooled to -70°C . Phenylacetylene (Note 19), 4.1 mL (37.1 mmol), is slowly added via a syringe through the rubber septum. After addition, the reaction mixture is maintained at -30°C to -25°C for 2 hr (Note 20), then recooled to -70°C and 6.8 g (15 mmol) of the previously prepared iodonium tosylate is added, in the solid form, through the side neck, over a positive argon pressure. The stirring reaction mixture is gradually warmed to room temperature and stirred for an additional 12 hr at room temperature. The mixture is poured into a 1-L beaker containing 200 mL of saturated ammonium chloride solution and stirred vigorously. The undissolved materials are filtered off and the organic phase is separated. The aqueous phase is extracted with three 50-mL portions of ether. The combined organic phase are washed with 100 mL of water followed by 100 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate and filtered. The solvent is removed on a rotary

evaporator in the hood and the residual oil chromatographed (4 x 50 cm column) on alumina (600 g, Note 21). The column is successively eluted with 1 L of hexane, 750 mL of 10% dichloromethane-hexane, 500 mL of 20% dichloromethane-hexane and 250 mL of 30% dichloromethane-hexane. The fractions are analyzed by TLC on silica gel (Note 22) using 10% dichloromethane-hexane as eluent and the product-containing fractions (Note 23) are combined. The solvent is evaporated on a rotary evaporator and the residual yellow-brown oil (5.8 g) (Note 24) is distilled under reduced pressure, bp 135-143°C (3-4 mm), to give 2.3 g of crude product. Redistillation under reduced pressure affords 1.9-2.1 g (53-58%) of product as a pale yellow liquid, bp 143-144°C (1 mm) (Note 25).

2. Notes

1. Many 1-trimethylsilylalkynes are commercially available from Aldrich, Petrarch and other vendors of silicon compounds. Alternatively they are readily made from 1-alkynes and chlorotrimethylsilane as described in part A.

2. 1-Hexyne was obtained from Tokyo Kasei Kogyo Co., Ltd. or Aldrich Chemical Company, Inc. and used without purification.

3. Tetrahydrofuran was obtained from Wako Pure Chemical Industries, Ltd., and distilled from potassium benzophenone ketyl immediately before use.

4. Butyllithium in hexane (2.6 M) was obtained from Mitsuwas Pure Chemical or Aldrich Chemical Company, Inc. and a freshly opened sample was used without assay or purification.

5. Chlorotrimethylsilane was obtained from Shin-ETSU Silicon Chemicals or PCR Research Chemicals, Inc., and distilled prior to use.

6. During this period copious amounts of a white precipitate (LiCl) is formed.

7. Iodosobenzene was purchased by the checkers from Tokyo Kasei Kogyo Co., Ltd. and dried under reduced pressure prior to use.

8. Chloroform was distilled from phosphorus oxide (P_2O_5) and passed through an alumina column prior to use.

9. Boron trifluoride etherate (98%) was obtained from Wako Pure Chemical Industries, Ltd., or MC and B Manufacturing Chemists, and distilled from granular calcium hydride prior to use.

10. The pale yellow suspension turns to a deeper yellow suspension during addition.

11. Iodosobenzene is a polymer and depolymerizes as it reacts, forming a clear, yellow-light brown, homogeneous solution during the course of the reaction. It is not ready for work-up until a clear homogeneous solution is obtained.

12. p-Toluenesulfonic acid monohydrate was obtained from Wako Pure Chemical Industries, Ltd., or MC and B Manufacturing Chemists, and used without further purification.

13. Care must be taken to release periodically the pressure formed. It is advisable to chill both solutions prior to mixing and shaking.

14. The spectral properties of 1-hexynyl(phenyl)iodonium tosylate are as follows: IR (nujol) cm^{-1} : 2185 (m, $C\equiv C$), 1225 (s), 1175 (m), 1145 (vs), 1115 (m), 1025 (m), 1000 (s), 985 (m, sh), 807 (m), 730 (m), 675 (s); FAB-MS m/z 285 (n, $BuC\equiv CIPh^+$); 1H NMR ($CDCl_3$) δ : 0.73-0.92 (m, CH_3), 1.12-1.58 (m, CH_2CH_2), 2.30 (s, $ArCH_3$), 2.30-2.50 (m, CH_2), 6.98-7.60 (m, ArH), 7.92-8.05 (m, ArH).

15. 1-Bromobutane was obtained from Wako Pure Chemical Industries, Ltd., or Eastman Kodak Company, and distilled through a 10-cm Vigreux column prior to use.

16. Copper(I) bromide-dimethyl sulfide complex, $(CuBr \cdot SMe_2)$, 99%, was obtained from Aldrich Chemical Company, Inc. and purified prior to use as follows: 10 g of $CuBr \cdot SMe_2$ was dissolved in 20 mL of dimethyl sulfide and triturated with 30 mL of

pentano. The resulting white crystals were filtered, washed with three 20-ml portions of pentane and dried under reduced pressure.

17. Dimethyl sulfide, 99+%, anhydrous, was obtained from Tokyo Kasei Kogyo Co., Ltd., or Aldrich Chemical Company, Inc.

18. The white suspension turned to an orange suspension during the course of the addition.

19. Phenylacetylene was obtained from Tokyo Kasei Kogyo Co., Ltd., or Farchan Laboratories and distilled through a 15-cm Vigreux column prior to use.

20. During this period the color changed from orange through brown to black.

21. Unactivated alumina from J. T. Baker Chemical Company was used.

22. TLC silica gel 60F₂₅₄ sheets were obtained from Merck & Company, Inc.

23. The desired product appears as the second spot on TLC with an $R_f = 0.42$ - 0.45 with 10% dichloromethane-hexane.

24. The major by-product is 5,8-diphenyldodeca-5,7-diene, which can be separated by distillation.

25. GC analysis of the product on a 10% UCW-982 Chromosorb W column (0.25 in x 6 ft) at 200°C showed a single isomer with a purity of 99%. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 3070 (m, sh), 3050 (m), 3015 (m), 2950 (vs), 2925 (vs), 2855 (s), 2200 (w), 1595 (m), 1570 (w), 1490 (m), 1465 (s), 1442 (s), 1375 (m), 1325 (m), 847 (m), 752 (vs), 690 (vs), MS (EI) m/z : 240 M^+ , 57%, 141 (100%), 105 (53%); ^1H NMR (CDCl_3) δ : 0.81-1.00 (m, CH_3), 1.21-1.59 (m, CH_2CH_2), 2.30-2.46 (m, CH_2), 2.67-2.84 (m, CH_2), 5.74 (t, $J = 2$, $\text{C}=\text{CH}$), 7.14-7.51 (m, ArH); ^{13}C NMR (300 MHz, CDCl_3) δ : 13.52 (CH_3), 13.81 (CH_3), 19.35 (CH_2), 21.91 (CH_2), 22.50 (CH_2), 30.50 (CH_2), 30.96 (CH_2), 31.70 (CH_2), 78.93 ($\text{C}\equiv\text{C}$), 95.47 ($\text{C}\equiv\text{C}$), 107.42 ($\text{C}=\text{CH}$), 125.78, 127.44, 128.24, 140.52 (aromatic), 151.88 ($\text{C}=\text{CH}$).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

The only known alternative procedure for the preparation of alkynyl(phenyl)iodonium arylsulfonates, the latest member of the family² of polyvalent iodine compounds, involves the reaction of [hydroxy(tosyloxy)iodo]benzene, $\text{PhIOH}\cdot\text{OTs}$, with terminal alkynes as first reported by Koser³ and elaborated by us.⁴ This procedure has a number of shortcomings. Formation of the desired alkynyliodonium salt is usually accompanied by a related vinyl species, $\text{R}(\text{TsO})\text{C}=\text{CHPh}\cdot\text{OTs}$, that both decreases the yields and causes purification problems. Furthermore, when the alkyl substituent of the starting alkyne is small, such as CH_3 , *n*-Pr, *n*-Bu, etc., this procedure gives either no product³ or low yields⁴ at best.

The present procedure, similar to that of Fujita⁵ for the preparation of alkynyl(phenyl)iodonium tetrafluoroborates, $\text{RC}\equiv\text{CPh}\cdot\text{BF}_4$, is simpler, much more general and in most cases gives significantly better yields.⁶ Table I gives yields of alkynyl(phenyl)iodonium sulfonates prepared by this procedure.

TABLE I
ALKYNYL(PHENYL)IODONIUM SULFONATES

Starting Alkyne	Product	Yields (%)	M.P. (dec.) °C
$\text{CH}_3\text{C}\equiv\text{CH}$	$\text{CH}_3\text{C}\equiv\text{CPh}\cdot\text{OTs}$	62	123-125
$\text{EtC}\equiv\text{CH}$	$\text{EtC}\equiv\text{CPh}\cdot\text{OTs}$	81	108-110
$n\text{-PrC}\equiv\text{CH}$	$n\text{-PrC}\equiv\text{CPh}\cdot\text{OTs}$	89	93-95
$\text{Me}_3\text{SiC}\equiv\text{CSiMe}_3$	$\text{Me}_3\text{SiC}\equiv\text{CPh}\cdot\text{OTs}$	70	107-109
$\text{PhC}\equiv\text{CH}$	$\text{PhC}\equiv\text{CPh}\cdot\text{OTs}$	61	128-133 ⁴
$t\text{-BuC}\equiv\text{CH}$	$t\text{-BuC}\equiv\text{CPh}\cdot\text{OTs}$	67	118-124 ⁴

Alkynyl(phenyl)iodonium sulfonates are stable, microcrystalline substances that can be stored and used indefinitely with little or no decomposition. They have been employed in the formation of aryl (2-furyl)iodonium tosylates,⁷ alkynyl sulfonate,⁴ carboxylate⁸ and phosphate⁹ esters, tricoordinate vinyliodine species,¹⁰ and alkylidenecarbene-iodonium ylides.¹¹

The stereoselective formation of conjugated enynes has been reported¹² via the coupling of vinylcopper reagents with alkynyl(phenyl)iodonium tosylates. A representative example of this process is described in part C of the present procedure. This method¹² affords stereoisomerically pure 1,1-disubstituted conjugated 1,3-enynes with a trisubstituted olefin component with complete control of olefin geometry. The simplicity of the procedure, mild reaction conditions, reasonable yields (46-94%) and total stereocontrol¹² should make this an attractive alternative and complement to the known^{13,14} Pd-catalyzed olefin-alkyne couplings for the synthesis of this important class of aliphatic compounds.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Hexynyl(phenyl)iodonium tosylate: Iodine, 1-hexynyl(4-methylbenzenesulfonato-O)phenyl- (11); (94957-42-3)

(E)-5-Phenyldodec-5-en-7-yne: Benzene, (1-butyl-1-octen-3-ynyl)-, (E)- (12); (111525-79-2)

1-Trimethylsilyl-1-hexyne: Silane, 1-hexynyltrimethyl- (8,9); (3844-94-8)

1-Hexyne (8,9); (693-02-7)

Chlorotrimethylsilane: Silane, Chlorotrimethyl- (8,9); (75-77-4)

Iodosobenzene: Benzene, iodoso- (8); Benzene, iodosyl- (9); (536-80-1)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃) (1:1) (8);

Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

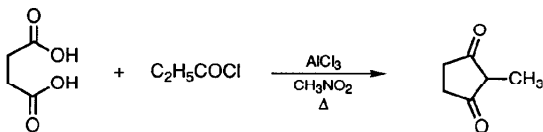
1-Bromobutane: Butane, 1-bromo- (8,9); (109-65-9)

Dimethyl sulfide: Methyl sulfide (8); Methane, thiobis- (9); (75-18-3)

Phenylacetylene: Benzene, ethynyl- (8,9); (536-74-3)

2-METHYL-1,3-CYCLOPENTANEDIONE

(1,3-Cyclopentanedione, 2-methyl-)



Submitted by Philip G. Meister, Matthew R. Sivik, and Leo A. Paquette.¹

Checked by David L. Coffen.

1. Procedure

Caution! These operations result in the evolution of considerable amounts of hydrogen chloride and should therefore be performed in a well-ventilated hood

A dry, 5-L, three-necked, round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer (Note 1), and an efficient reflux condenser (Note 2) is charged with 500 mL of dry nitromethane (Note 3). Stirring is begun and 1000 g (7.50 mol) of anhydrous aluminum chloride (Note 4) is added, followed by an additional 500 mL of dry nitromethane. After the reaction mixture cools to room temperature, the gas inlet is replaced with a Gooch tube attached to a 500-mL filter flask containing 295 g (2.5 mol) of powdered succinic acid (Note 5). The nitrogen line is now attached to the sidearm of this flask. The succinic acid is introduced in portions during 1.5 hr (*Caution: This process evolves a large volume of hydrogen chloride gas which may cause the mixture to foam. Small quantities of the acid should be added at a time and the foaming should be allowed to subside prior to introduction of the next amount*). The mixture is stirred for 2 hr and the Gooch tube is replaced by a 500-mL pressure-equalizing addition funnel equipped with a nitrogen inlet. Propionyl chloride (650 mL,

694 g, 7.5 mol) (Note 6) is added dropwise during 30 min and the reaction mixture is brought to reflux for 2 hr, cooled, and poured onto 4 L of crushed ice. After the precipitated brown solid is cooled in an ice bath, it is separated by filtration (Note 7) and washed with 250 mL of brine and 250 mL of cold (0°C) toluene. The material is dissolved in 7 L of boiling water containing 20 g of decolorizing carbon, then filtered while still hot (Note 8). The filtrate is concentrated to a volume of 5 L, then cooled in an ice bath. The crystals are collected by suction filtration and air-dried to give 157-171 g (56-61%) of 2-methyl-1,3-cyclopentanedione (Note 9). The mother liquors are concentrated to approximately 1.5 L by rotary evaporation. The solution is boiled until crystals form, cooled in ice, and filtered to give an additional 20-23 g (7-8%) of product (63-69% overall yield).

2. Notes

1. Efficient stirring is mandatory.
2. *The top of the condenser is equipped with a gas outlet leading via an oil bubbler into a large alkali bath or to a water aspirator. A steady stream of nitrogen should be maintained at all times.*
3. Commercial nitromethane was dried over calcium chloride, filtered, and distilled. The forerun was discarded. The checker used 96% spectrophotometric grade as received from Aldrich Chemical Company, Inc.
4. Aluminum chloride, which was obtained from Fluka Chemical Corporation, generates heat during dissolution.
5. Succinic acid was obtained in powdered form from Fluka Chemical Corporation. If granular succinic acid is to be used, it should be pulverized to aid in dissolution.

6. Propionyl chloride was purchased from Fluka Chemical Corporation and Aldrich Chemical Company, Inc.

7. Two 17-cm Büchner funnels should be used simultaneously. However, if left to digest overnight, the mixture can be conveniently filtered using a 3-L sintered glass funnel.

8. Use of a 17-cm Büchner funnel preheated with hot tap water has proven most convenient for this purpose. The checker used an oven-heated, 3-L sintered glass funnel layered with Celite.

9. The crystals are off-white to tan, mp 211-212°C.

Waste Disposal Information

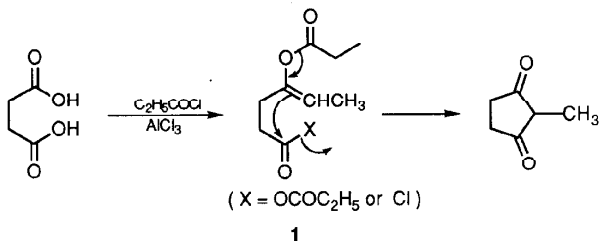
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

A variety of methods have been published to achieve the preparation of 2-methyl-1,3-cyclopentanedione.²⁻⁶ The present method, which was first reported by Schick, Lehmann, and Hilgetag,⁴ provides for the acquisition of large amounts of the product in a single step from inexpensive starting materials. The alternative multistep procedures are appreciably more laborious and costly.

The importance of the title compound as an intermediate in organic synthesis goes unquestioned, having been produced on an industrial scale. The syntheses and reactions of this class of compounds have recently been summarized in an extensive review of the subject.⁷

The success of the present process appears to rest on the facility with which intermediate **1** is produced and its capacity for ready intramolecular cyclization.⁴



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Methyl-1,3-cyclopentanedione: 1,3-Cyclopentanedione, 2-methyl- (8,9); (765-69-5)

Aluminum chloride (8,9); (7446-70-0)

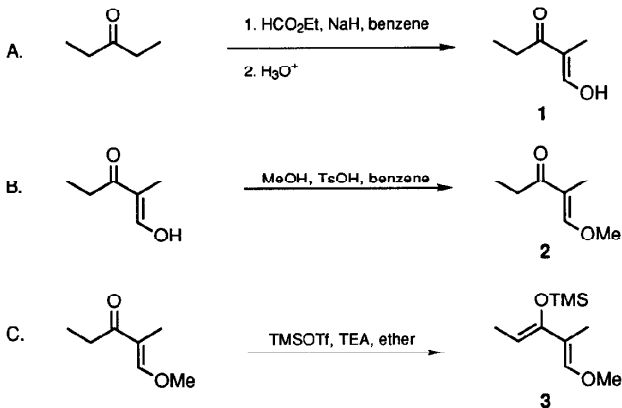
Nitromethane: Methane, nitro- (8,9); (75-52-5)

Succinic acid (8); Butanedioic acid (9); (110-15-6)

Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

PREPARATION OF (E,Z)-1-METHOXY-2-METHYL-3-(TRIMETHYLSILOXY)-
1,3-PENTADIENE

(Silane, [[1-(2-methoxy-1-methylethenyl)-
1-propenyl]oxy]trimethyl-, (Z,E)-)



Submitted by David C. Myles and Mathew H. Bigham.^{1,2}

Checked by David I. Magee and Robert K. Boeckman, Jr.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. A 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, calcium sulfate drying tube, and 500-mL pressure equalizing addition funnel is charged with 2.4 L of dry benzene (Note 1), 81.7 g (2.04 mol) of 60% sodium hydride

dispersion in benzene (Note 2), and 1.9 mL (0.05 mol) of methyl alcohol (Note 3). The flask is immersed in an ice bath and the addition funnel is charged with a mixture (Note 4) of 222 mL (172 g, 2 mol) of 95% 3-pentanone and 163 mL (148 g, 2 mol) of 99% ethyl formate (Note 5). This mixture is added dropwise to the cooled, stirred suspension over 1.5 hr. During the addition, there is a visible evolution of gas, the mixture darkens, and a paste-like precipitate forms. At the completion of the addition, the ice bath is removed and the mixture is stirred an additional 1.5 hr, until gas evolution has ceased. The stirred reaction mixture is then diluted with 1.5 L of anhydrous ether (Note 6). The suspension is filtered through an 18.5-cm Büchner funnel fitted with two Whatman 1 filter papers and the solid is washed with two 500-mL portions of anhydrous ethyl ether. The solid is transferred to a 19 x 10-cm evaporating dish and dried under reduced pressure in a vacuum desiccator to afford crude sodium salt of **1** (270-280 g) as a colorless or slightly tan hygroscopic solid. The material is carried on directly in the continuation of this procedure.

A 4-L Erlenmeyer flask equipped with a 2-in Teflon-coated magnetic stirbar is charged with 1.5 L of deionized water and placed in an ice bath. To the stirring water is added in small portions (*Caution*, Note 7) the crude sodium salt of **1**. When all of the salt has dissolved, the cooled, dark brown solution is acidified to pH 5 (Hydron paper) by dropwise addition of concd hydrochloric acid. The resultant two-phase mixture is poured into a 3-L separatory funnel and the Erlenmeyer flask is washed with two 100-mL portions of ethyl ether which are added to the separatory funnel. An additional 800 mL of ether is added to the mixture. The upper (organic) and lower (aqueous) phases are separated. The aqueous phase is extracted six additional times (Note 8) with 400 mL of ether each time. The combined organic phases are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure at 10°C to afford approximately 250 mL of crude **1** as a clear amber oil. This is distilled (Note 9) under reduced pressure (bp 58.5°C, 20 mm) to afford 125-137 g (55-60% yield) of **1**

as a slightly yellow oil which solidifies on standing. An analytical sample of **1** was prepared by recrystallization from pentane (mp 42-43°C) (Note 10).

B. A 3-L, three-necked, round-bottomed flask is equipped (see Figure 1) with a 2-in Teflon-coated magnetic stirring bar, a 150-mm Vigreux column topped by a 500-mL pressure-equalizing addition funnel and calcium sulfate drying tube, a short path distillation apparatus, and a ground glass stopper. The flask is charged with 1 L of benzene and 0.5 L of a 60:40 mixture of benzene/methanol (Note 11). To this solution is added 114 g (1.0 mol) of 1-hydroxy-2-methylpent-1-en-3-one (**1**) in a small amount of benzene and 0.95 g (0.005 mol) of p-toluenesulfonic acid monohydrate. The addition funnel is charged with 500 mL of the 60:40 benzene/methanol mixture. The magnetically stirred solution is warmed to a gentle reflux at which time the solution begins to darken to a light brown color. The distillation temperature rises to 59°C (the boiling point of the benzene/methanol azeotrope) and stabilizes. The distillate volume is monitored throughout the course of the reaction. When 250 mL of distillate has collected, the reaction vessel is replenished with 250 mL of fresh benzene/methanol mixture. *This cycle is repeated 6 times until starting material is consumed* (Note 12). At this time any residual benzene/methanol mixture in the addition funnel is discarded and the funnel is charged with 500 mL of benzene. The reaction volume is maintained by the addition of benzene as the boiling point of the distillate rises to 79°C. In this way, a total of 750 mL of benzene is distilled out of the reaction mixture as the reaction is driven to completion. The reaction mixture is allowed to cool to room temperature and is quenched by the addition of 500 mL of 1.0 M aqueous sodium bicarbonate solution. The two phase mixture is stirred for 5 min and then transferred to a 2-L separatory funnel. The phases are separated and the aqueous (lower) phase is extracted two times with 500 mL of ether each time. The combined organic phases are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give crude **2** as a brown oil. The oil is fractionally distilled under reduced

pressure (bp 94-96°C, 22 mm) to afford 90-96 g (70-75%) of **2**. Assay of this material by GLC shows it to be ca. 95% pure (Note 13).

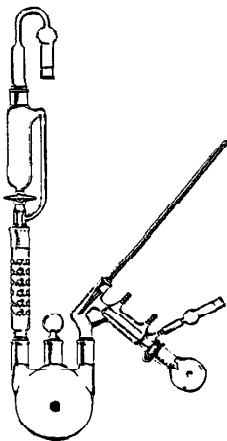


Figure 1

C. A 2-L, round-bottomed flask equipped with a 2-in Teflon-coated magnetic stirring bar is charged with 750 mL of anhydrous ether, 102 g (1.0 mol) of 99% triethylamine (Note 14) and 96 g (0.75 mol) of 1-methoxy-2-methylpent-1-en-3-one (**2**). The flask is capped with a rubber septum equipped with a 16-gauge needle connected to a dry nitrogen source. The magnetically stirred solution is cooled in an ice bath and 167 g (0.75 mol) of trimethylsilyl trifluoromethanesulfonate (Note 15) is added via an 18-gauge cannula over 10 min. The cooled mixture is stirred for 30 min, during which time a red-brown oily precipitate forms. The reaction mixture is transferred to a 2-L separatory funnel and the red-brown (lower) phase is separated and discarded. The remaining ethereal phase is washed with 500 mL of 1.0 M

aqueous sodium bicarbonate solution and separated. The aqueous (lower) phase is extracted with 500 mL of ether, separated and discarded. The combined organic phases are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield crude diene **3** as a yellow oil. This is fractionally distilled through a 150-mm Vigreux column at reduced pressure (bp 83-85°C, 22 mm) to afford 121-131 g (81-87%) of **3** as a colorless or slightly yellow liquid. Assay of this material by GLC shows it to be ca. 95% pure (Note 16).

2. Notes

1. Unless otherwise indicated, the solvents are reagent grade and are used without further purification.

2. Commercially available (Aldrich Chemical Company, Inc.) 60% sodium hydride dispersed in mineral oil is dispersed in benzene in the following manner: 81.7 g of 60% sodium hydride mineral oil dispersion is suspended in 100 mL of benzene in a 500-mL Erlenmeyer flask equipped with a Teflon-coated magnetic stirbar. The suspension is vigorously stirred for 1 hr until all of the lumps are gone. The suspension is then transferred to the reaction vessel with a small amount of benzene.

3. Methyl alcohol functions as a catalytic base in this reaction.

4. The efficiency of the procedure is enhanced by complete premixing of the 3-pentanone and ethyl formate.

5. 3-Pentanone and ethyl formate were purchased from Aldrich Chemical Company, Inc. and used without further purification.

6. Efficient mixing is essential during the addition of the ether to ensure the formation of a flocculent precipitate. Inadequate agitation results in the formation of large clumps of product.

7. *Caution:* Small amounts of sodium hydride from the previous step may remain in the solid. The addition should be carried out slowly enough to allow any residual sodium hydride to quench completely before the next portion of solid is added.

8. TLC analysis (Merck 0.25-mm silica gel plates with 254 nm UV indicator, 1:4 ethyl acetate:hexanes) of the organic phase of each extraction reveals the presence of **1** ($R_f = 0.32$). Extraction is continued until **1** is no longer seen in the organic extracts.

9. Crude **1** may solidify in the pot as any remaining solvent evaporates, but can be reliquified by gentle heating. Stirring is facilitated by a powerful magnetic stirrer and 2-in Teflon-coated magnetic stirbar. To prevent solidification of the distillate on the condenser, the water temperature through the condenser is maintained at 25°C. To minimize product loss, all fractions were collected in a receptacle cooled with an ice bath.

10. The $^1\text{H-NMR}$ spectrum of **1** is as follows: (90 MHz, CDCl_3 , TMS = 0 ppm) δ : 1.13 (t, 3 H, $J = 7$), 1.79 (s, 3 H), 2.46 (q, 2 H, $J = 7$), 7.45 (s, 1 H), 7.57 (s, 1 H).

11. The composition of the binary azeotrope of benzene and methanol is 60.5% benzene, 39.5% methanol.

12. The progress of the reaction is monitored by TLC (R_f of **1** = 0.32, R_f of **2** = 0.25; 1:4 ethyl acetate:hexanes). A non-UV absorbing spot ($R_f = 0.29$) is seen to form as an intermediate between **1** and **2**. This is presumed to be the 1,1-dimethyl acetal of **1**. When this spot is nearly gone, the reaction is presumed to be complete.

13. The $^1\text{H-NMR}$ of **2** is as follows: (90 MHz, CDCl_3 , TMS) δ : 1.10 (t, 3 H, $J = 7.4$), 1.71 (s, 3 H), 2.52 (q, 2 H, $J = 7.4$), 3.86 (s, 3 H), 7.23 (bs, 1 H).

14. Triethylamine was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

15. Trimethylsilyl trifluoromethanesulfonate was purchased from Petrarch Systems and was used without further purification.

10. The $^1\text{H-NMR}$ of **3** is as follows: (90 MHz, CDCl_3 , CHCl_3 , δ 7.27) δ : 0.23 (s, 9 H), 1.63 (d, 3 H, $J = 7$), 1.70 (s, 3 H), 3.66 (s, 3 H), 4.75 (q, 1 H, $J = 7$), 6.35 (s, 1 H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Siloxy dienes have been shown to be highly effective in both the Diels-Alder³ reaction and the hetero Diels-Alder (diene-aldehyde cyclocondensation)⁴ reactions. Diene **3** has been used in the synthesis of several important natural products including zincophorin,⁵ rifamycin,⁶ and the Prelog-Djerassi lactone.⁷ Recently, under the aegis of chiral catalysts, **3** has been shown to participate in the diene-aldehyde cyclocondensation reaction with several aldehydes to afford cycloadducts of very high enantiomeric excess.⁸

The procedure described here allows the convenient preparation of large quantities of diene **3** and has several advantages over previously published sequences. 1-Methoxy-2-methylpenten-3-one (**2**) can be prepared in ca. 90-g lots and can be stored for several months at 0°C under argon. The earlier procedure for the synthesis of **2**⁹ relies on dimethyl sulfate as the methylating reagent in the formation of the methyl enol ether moiety. The high toxicity of this reagent renders this strategy unattractive for routine use. The published procedure for the conversion of **2** to 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene (**3**)^{3a} uses trimethylsilyl chloride, triethylamine and a catalytic amount of zinc chloride in benzene (40°C, ca. 12

hr) for the silylation. This mixture results in the formation of copious quantities of triethylamine hydrochloride, which greatly complicates the work up and purification. This new procedure, using trimethylsilyl trifluoromethanesulfonate and triethylamine, allows the convenient separation of the amine salt and significantly shortens the reaction time (30 min vs 12 hr). The silylation can be carried out on scales ranging from 0.10 mol to 0.75 mol with consistently good yields. Diene **3** can be stored for several months at 0°C under argon without significant decomposition.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(E,Z)-1-Methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene: Silane, [[1-(2-methoxy-1-methylethenyl)-1-propenyl]oxy]trimethyl-, (Z,E)- (10); (72486-93-2)

Sodium hydride (8,9); (7646-69-7)

3-Pentanone (8,9); (96-22-0)

Ethyl formate: Formic acid, ethyl ester (8,9); (109-94-4)

1-Hydroxy-2-methylpent-1-en-3-one: 1-Penten-3-one, 1-hydroxy-2-methyl- (9); (50421-81-3)

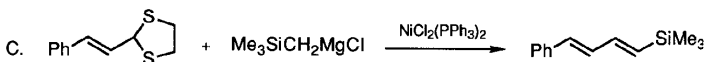
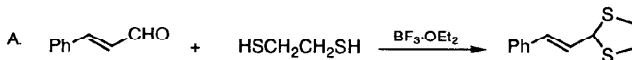
p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

Trimethylsilyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, trimethylsilyl ester (8,9); (27607-77-8)

NICKEL-CATALYZED SILYLOLEFINATION OF ALLYLIC DITHIOACETALS:

(E,E)-TRIMETHYL(4-PHENYL-1,3-BUTADIENYL)SILANE

(Silane, trimethyl (4-phenyl-1,3-butadienyl)-, (E,E)-)



Submitted by Zhi-Jie Ni and Tien-Yau Luh.¹

Checked by Shigeki Habaue and Hisashi Yamamoto.

1. Procedure

Caution! 1,2-Ethanedithiol has a powerful stench. Steps A and C should be performed in a well-ventilated hood.

A. *2-(2-Phenylethenyl)-1,3-dithiolane.* In a 1-L, round-bottomed flask equipped with a magnetic stirring bar are placed 26.8 g (0.2 mol) of freshly distilled (E)-3-phenyl-2-propenal and 20.1 g (0.21 mol) of 1,2-ethanedithiol in 400 mL of chloroform. To the stirred solution is added 10 mL (11.3 g, 0.080 mol) of boron trifluoride etherate in one portion. The mixture is stirred at room temperature for 2 hr. The chloroform solution is washed with two 100-mL portions of 10% aqueous sodium hydroxide. The aqueous

layer is extracted twice with 100 mL of chloroform. The combined organic layers are washed twice with 200 mL of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate is concentrated under reduced pressure to give 40.6 g (97%) of a white solid which is sufficiently pure for the next operation.

B. (Trimethylsilyl)methylmagnesium chloride. A 500-mL, three-necked, round-bottomed flask containing 5.2 g (0.22 g-atom) of magnesium turnings is equipped with a rubber septum, a reflux condenser, an addition funnel and a magnetic stirring bar. The system is flame-dried and flushed with nitrogen. A few crystals of iodine and 150 mL of anhydrous ether (Note 1) are introduced. As the contents of the flask are stirred, 25.8 g (0.21 mol) of (chloromethyl)trimethylsilane (Note 2) is added in small portions until the reaction begins, and then at such a rate as to maintain gentle refluxing of the ether. The addition requires about 30 min, after which the mixture is heated under reflux for an additional 30 min. The solution is cooled to room temperature and is used directly for the next reaction.

C. (E,E)-Trimethyl(4-phenyl-1,3-butadienyl)silane. In a 1-L, two-necked, round-bottomed flask fitted with a reflux condenser, rubber septum, and a magnetic stirring bar are placed 14.6 g (0.070 mol) of 2-(2-phenylethenyl)-1,3-dithiolane and 2.3 g (0.0035 mol) of dichlorobis(triphenylphosphine)nickel (Note 3). The flask is evacuated and flushed with nitrogen three times. To the above mixture is added 200 mL of anhydrous tetrahydrofuran (Note 4); then it is cooled in an ice bath. The ether solution of (trimethylsilyl)methylmagnesium chloride prepared above is introduced with a double-ended needle in one portion (Note 5). The mixture is refluxed for 10 hr, cooled to room temperature, and treated with 200 mL of saturated ammonium chloride solution. The organic layer is separated and the aqueous layer is extracted with three, 200-mL portions of ether. The combined organic layers are washed twice with 100 mL of aqueous 10% sodium hydroxide solution and twice with 100 mL of brine. The organic solution is dried over anhydrous magnesium sulfate. The solvent is removed

under reduced pressure and the residue is filtered through a short column packed with 30 g of silica gel (Note 6) and flushed under a positive nitrogen pressure with 300 mL of hexane. After evaporation of the solvent under reduced pressure, the yellowish residue is distilled to give 12.9 g (91%) of (E,E)-trimethylsilyl(4-phenyl-1,3-butadienyl)silane (Note 7) as a colorless liquid, bp 99-101°C (0.6 mm), which solidifies on standing, mp <37°C.

2. Notes

1. Ethyl ether is distilled from sodium-benzophenone ketyl before use.

2. (Chloromethyl)trimethylsilane, also available from Aldrich Chemical Company, Inc., was purchased from Wako Pure Chemical Industries, LTD. and used directly.

3. Dichlorobis(triphenylphosphine)nickel, also available from Aldrich Chemical Company, Inc., was purchased from Fluka AG, and used without further purification. The catalyst can also be prepared according to literature procedures.²

4. Tetrahydrofuran is distilled from sodium-benzophenone ketyl before use.

5. An excess of the Grignard reagent is required to maximize the yield; otherwise, the reaction is incomplete.

6. Silica gel (230-400 mesh) was purchased from E. Merck Co.

7. The spectral properties of the product are as follows: IR (neat) cm^{-1} : 3040, 1605, 1450, 1250, 1000, 870, 840, 730, 690; ^1H NMR (CDCl_3) δ : 0.13 (s, 9 H, $-\text{Si}(\text{CH}_3)_3$), 6.01 (d, 1 H, $J = 17.6$, $=\text{CHTMS}$), 6.58 (d, 1 H, $J = 15.2$, PhCH=), 6.69 (dd, 1 H, $J = 9.8$ and 17.6 , $-\text{CH=CHTMS}$), 6.83 (dd, 1 H, $J = 9.8$ and 15.2 , PhCH=CH-), 7.20-7.40 (m, 5 H, aromatic) (The assignments for olefinic protons are based on simulation results); ^{13}C NMR (CDCl_3) δ : -1.5, 126.7, 127.8, 128.7, 131.8, 133.0, 135.2, 137.4, 144.3; exact mass calcd for $\text{C}_{13}\text{H}_{18}\text{Si}$: 202.1178; found 202.1185.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories": National Academy Press: Washington, DC. 1983.

3. Discussion

Trimethyl(4-phenyl-1,3-butadienyl)silane can be prepared by the reaction of bis(trimethylsilyl)methylolithium with cinnamaldehyde³ or 1,3-bis(trimethylsilyl)propenylolithium with benzaldehyde.^{4,5} The reaction of 1-bromo-2-phenylthioethene with (E)-2-trimethylsilylethenylmagnesium bromide in the presence of a palladium catalyst gives the corresponding dienyl sulfide which serves as a precursor for the preparation of butadienylsilanes.⁶ However, the starting materials in most of these syntheses are not readily available.

The procedure described here is based on a series of reports on the nickel-catalyzed coupling reactions of dithioacetals with Grignard reagents.⁷⁻¹¹ The method offers a new, very efficient and convenient route to the substituted butadienylsilanes.⁷ The starting materials are easily accessible and the operation is very simple. The reaction in general is highly stereoselective, if not stereospecific. The phenyl substituent can be replaced with simple alkyl groups and yields essentially remain unchanged.⁷ The extension of this method to the synthesis of trienylsilanes has proved successful.⁷ Since vinylsilanes can be converted into α,β -unsaturated aldehydes,¹²⁻¹⁶ the combination of these latter procedures with the method described here can be used in the homologation of enals. (E)- β -Arylvinylsilanes are synthesized stereospecifically in a similar manner from benzylic dithioacetals.⁸

1. Department of Chemistry, The Chinese University of Hong Kong, Shatin, N. T., Hong Kong, and Department of Chemistry, National Taiwan University, Taipei, Taiwan, Republic of China.
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Appendix

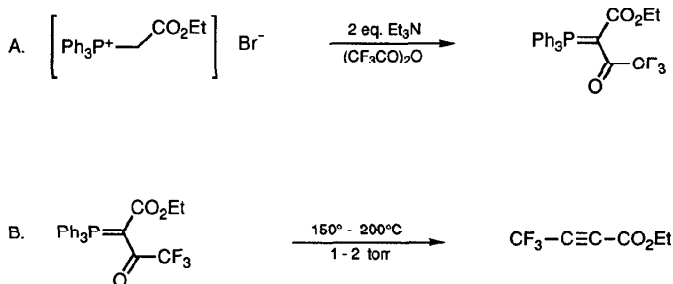
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (E,E)-Trimethyl(4-phenyl-1,3-butadienyl)silane: Silane, trimethyl(4-phenyl-1,3-butadienyl)-, (E,E)- (10); (70960-88-2)
- 1,2-Ethanediol (8,9); (540-63-6)
- 2-(2-Phenylethenyl)-1,3-dithiolane: 1,3-Dithiolane, 2-styryl- (8); 1,3-Dithiolane, 2-(2-phenylethenyl)- (9); (5616-58-0)
- (E)-3-Phenyl-2-propenal: Cinnamaldehyde (E)- (8); 2-Propenal, 3-phenyl-, (E)-(9); (14317-10-9)
- Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)
- (Trimethylsilyl)methylmagnesium chloride: Magnesium, chloro[(trimethylsilyl)methyl]- (8,9); (13170-43-9)
- Chloromethyltrimethylsilane: Silane, (chloromethyl)trimethyl- (8,9); (2344-80-1)
- Dichlorobis(triphenylphosphine)nickel: Nickel, dichlorobis(triphenylphosphine)- (8,9); (14264-16-5)

α -ACETYLENIC ESTERS FROM α -ACYLMETHYLENEPHOSPHORANES:

ETHYL 4,4,4-TRIFLUOROTETROLATE

(2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester)



Submitted by B. C. Hamper.¹

Checked by T. Harrison and Larry E. Overman.

1. Procedure

A. *Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate.* A 2-L, four-necked, round-bottomed flask is equipped with a nitrogen line attached to a bubbler, a 250-mL pressure-equalizing funnel, an overhead stirrer and a thermometer. The flask is charged with 215 g (0.5 mol) of (carbethoxymethyl)triphenylphosphonium bromide and 1.1 L of anhydrous tetrahydrofuran (THF) (Notes 1 and 2). The stirred suspension is cooled in an ice water bath and treated with 150 mL (1.1 mol) of triethylamine (Note 3) added dropwise over 5 min. After the mixture is stirred for an additional 30 min at 5°C, it is treated dropwise with 78 mL (116 g, 0.55 mol) of trifluoroacetic anhydride (Note 4) in such a manner that the reaction temperature is

maintained between 5-10°C, which results in a total addition time of approximately 1 hr. The mixture is allowed to stir for 2 hr and subsequently filtered, the precipitate is washed three times with cold THF and the filtrate is concentrated under reduced pressure to afford a yellow oily residue. Trituration of the residue with 600 mL of water affords a crystalline product which is collected, washed three times with 100 mL of water, and dried by suction to afford 208 g of a yellowish colored solid (Note 5). The solid is dissolved in 900 mL of hot methanol, filtered, the solution treated with 500 mL of water and placed in a refrigerator overnight. The crystalline product is collected, washed three times with 100 mL of cold water and dried under reduced pressure to afford 200-208 g (89-93%) of ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)-acetoacetate as a very pale-yellow, crystalline solid (Note 6).

B. Ethyl 4,4,4-trifluorotetrolate. A 1-L, three-necked, round-bottomed flask is equipped with an efficient magnetic stirrer, a heating mantel, a thermocouple (Note 7) and a large bore gas exit tube (Figure 1, Note 8). To this flask are added 200 g (0.45 mol) of ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate and 40 g of potassium carbonate (Note 9). The gas exit tube is connected to a Dewar condenser, *modified with a side arm connection, which has a round-bottomed flask for collection of the product in a dry ice-acetone bath.* A second trap is placed between the reaction setup and the vacuum pump, all the traps are cooled with dry ice-acetone, and the system is evacuated to 1-2 mm. The reaction flask is carefully heated to 150°C (Note 10) at which point the phosphorane melts and the acetylene evolution begins. The molten phosphorane is stirred and heated from 160°C to 220°C over a period of 5 hr. Heating is carefully increased during the reaction in order to control the rate of distillation of the acetylenic product. From the round-bottomed flask in the cold trap is obtained 65-67 g (87-89%) of a clear, slightly yellow, liquid. The thermolysis product is dried with magnesium sulfate and filtered through Celite. Distillation at atmospheric pressure through a short-path distillation apparatus affords about 1.0 g of forerun and

59-61 g (79-82%) of ethyl 4,4,4-trifluorotetrolate as an analytically pure, colorless liquid, bp₇₆₀ 97-100°C (Note 11).

2. Notes

1. Anhydrous tetrahydrofuran was obtained from Aldrich Chemical Company, Inc., in SureSeal bottles and was used without further purification. (Carbethoxymethyl)triphenylphosphonium bromide may be obtained from Aldrich Chemical Company Inc., or prepared as described in *Org. Synth., Coll. Vol. VII* **1990**, 232. The in situ preparation described in Note 2 was used by the checkers.

2. We have found it more convenient to prepare (carbethoxymethyl)-triphenylphosphonium bromide in situ in the same reaction vessel from triphenylphosphine and ethyl bromoacetate. This effectively provides a one-pot preparation for the α -acylmethylenephosphorane from triphenylphosphine and allows facile incorporation of various esters, by employing different bromoacetate esters, in the acetylenic product. The yield and purity of the resultant phosphorane is unaffected by the following one-pot procedure.

A 2-L, four-necked, round-bottomed flask is equipped with a nitrogen line attached to a bubbler, a 250-mL pressure-equalizing funnel, an overhead stirrer and a thermometer. The flask is charged with 132 g of triphenylphosphine (0.503 mol) and 500 mL of anhydrous tetrahydrofuran and cooled in an ice water bath to 5°C. The stirred solution is treated dropwise with 56 mL of ethyl bromoacetate (84 g, 0.503 mol) added at such a rate that the temperature is maintained between 8°C and 10°C. The total addition time is about 15 min. After the mixture is stirred overnight, it is diluted with an additional 600 mL of anhydrous tetrahydrofuran and the precipitate is washed from the sides of the flask. The resultant suspension of (carbethoxymethyl)triphenyl-

phosphonium bromide is cooled in an ice-water bath and used directly in the same pot to prepare α -acylmethylenephosporanes as detailed in section A.

3. Triethylamine was supplied by Eastman Kodak Company and Fisher Scientific Company.

4. Trifluoroacetic anhydride was obtained from Aldrich Chemical Company, Inc.

5. The yellow crystalline solid is analytically pure (>95% by NMR and HPLC analysis), mp 124-127°C. We have found that the yield of the acetylenes can be adversely affected by small amounts of impurities in the α -acylmethylene-phosporanes and prefer to recrystallize the phosphoranes prior to thermolysis. The yield from the recrystallization step is greater than 95%.

6. The phosphorane softens above 120°C and melts between 125-130°C (lit.^{2,3} mp 125-127°C). Spectral properties of the phosphorane are as follows: ^1H NMR (500 MHz, CDCl_3) δ : 0.87 (t, 3 H, $J = 7.2$), 3.81 (q, 2 H, $J = 7.2$), 7.49 (dt, 6 H, $J = 7.9, 3.3$), 7.57 (m, 3 H), 7.67 (dd, 6 H, $J = 12.9, 7.9$); ^{13}C NMR (125 MHz, CDCl_3) δ : 13.5, 59.8, 70.1 (d, $^1J_{\text{CP}} = 110$), 117.9 (dd, $^1J_{\text{CF}} = 288$, $^3J_{\text{CP}} = 14.6$), 123.7 (d, $^1J_{\text{CP}} = 93.3$), 128.8 (d, $^2J_{\text{CP}} = 13.0$), 132.2 (d, $^4J_{\text{CP}} = 3.0$), 133.2 (d, $^3J_{\text{CP}} = 10.0$), 165.6 (d, $^2J_{\text{CP}} = 13.0$), 174.4 (dd, $^2J_{\text{CF}} = 34.0$, $^2J_{\text{CP}} = 5.8$); ^{31}P NMR (202 MHz, CDCl_3) δ : 19.8. Anal. Calcd for $\text{C}_{24}\text{H}_{20}\text{O}_3\text{F}_3\text{P}$: C, 64.87; H, 4.54. Found: C, 64.96; H, 4.60.

7. A stainless steel-covered thermocouple is preferred since it is less likely to break than a mercury thermometer. As the phosphorane begins to melt, large chunks of solid remain as the mixture is initially stirred, and these can lodge between a thermometer and the walls of the flask. The thermocouple has the added advantage that the steel rod can be used to help break up the melting phosphorane, taking care to avoid breaking the flask.

8. The large bore gas exit tube (Figure 1) used between the reaction flask and the Dewar condenser is a glass tee equipped with the appropriate 24/40 ground glass joints. Alternatively, the connection can be made using large bore, thick wall Tygon or vacuum tubing.

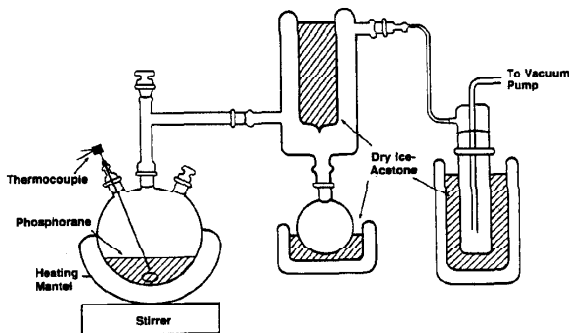


Figure 1

9. In the absence of potassium carbonate, the thermolysis product is slightly acidic and the pH of a water wash of freshly collected product is about 1.

10. *Caution! Care must be taken not to heat the phosphorane too rapidly, particularly before the solid has melted. The temperature of the molten material is not at equilibrium until the mixture has completely melted. If it is heated too rapidly, it is difficult to control the rate of acetylene production. It is best to heat slowly until a stirred, molten material is obtained and to continue heating at such a rate as to control acetylene formation. We have obtained excellent results applying initially 30 volts to a 380-watt, 115-volt, 1-L heating mantle obtained from Glas-Col Apparatus Company. Alternatively, more even and controlled heating can be obtained by using a large oil bath.*

11. Previous literature reports³ bp 96-98°C. Spectral properties of the acetylene are as follows: ¹H NMR (500 MHz, CDCl₃) δ: 1.34 (t, 3 H, J = 7.1), 4.32 (q, 2H, J = 7.1); ¹³C NMR (125 MHz, CDCl₃) δ: 13.8, 63.5, 69.9 (q, ²J_{CF} = 54.0), 75.5 (q, ³J_{CF} = 6.0), 113.4 (q, ¹J_{CF} = 259), 150.7; IR (neat) cm⁻¹: 2987, 2275 (w); 1731. Anal. Calcd for C₆H₅O₂F₃: C, 43.49; H, 3.03. Found: C, 43.14; H, 3.07.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Thermolysis of α-acylmethylenephosphoranes is the most convenient method for preparation of acetylenes with perfluoroalkyl substituents.^{3,4} Many of these acetylenes, particularly the trifluoromethyl analogs, are particularly volatile and thermolysis allows preparation and collection of material which is free of solvents or impurities of similar boiling point. In addition, the acetylenes are prepared from readily available starting materials with overall conversions for the two steps of greater than 75% in many cases. Attempts to prepare trifluorotetrolic acid by carbonylation of the lithium acetylenide of 3,3,3-trifluoropropyne have been unsuccessful.⁵ However, the treatment of lithium acetylenides with chloroformates affords perfluoroalkyl-substituted propiolates (the perfluoroalkyl group is a C₄ chain length or longer) in 38-43% yield along with an unusual by-product.⁶ Benzyl trifluorotetrolate, which was employed in the synthesis of a trifluoromethyl analog of geraniol, has been prepared from ethyl trifluoroacetoacetate via a pyrazolone in an overall yield of 55%.⁷ A number of

(difluoroalkyl)propiolates, employed in Diels-Alder cycloaddition reactions, have been prepared by treatment of the corresponding ketones with diethylaminosulfur trifluoride (DAST).⁸ The corresponding (difluoroalkyl)propionic acids have also been prepared by carbonylation of the magnesium bromoacetylide.⁹

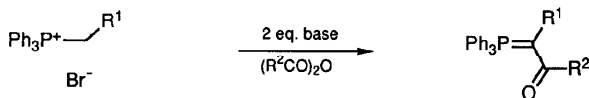
The utility of the phosphorane route to electron-deficient acetylenes depends on the facile synthesis of the α -acylmethylenephosphorane intermediates. Previously they had been prepared by a two-step procedure from the available phosphonium salts, requiring isolation of the Wittig reagent [e.g., (ethoxycarbonylmethylene)-triphenylphosphorane] intermediate.^{3,4} Acylation of the Wittig reagent affords, via transylidation,¹⁰ a 1:1 mixture of components which must be separated prior to thermolysis. In addition, at least half of the Wittig reagent is lost by conversion to the starting phosphonium salt. The addition of a suitable base, such as triethylamine, to the reaction mixture avoids the undesired transylidation reaction and affords complete conversion to the desired α -acylmethylenephosphorane. For acyl halides which have an acidic hydrogen α to the carbonyl group, treatment with base can give rise to ketenes which readily react with Wittig reagents to afford allenes.¹¹ This route, using triethylamine as a base, has been explored to prepare allenes that are either substituted or unsubstituted in the α -position.

For acyl halides or anhydrides which do not afford ketenes in the presence of base (such as perfluoroacyl halides), however, the α -acylmethylenephosphoranes can be prepared directly in one step from the phosphonium salts by using two equivalents of base by the present procedure (Table I).² Both tetrahydrofuran and methylene chloride have been used as solvents and in the case of the title compound, tetrahydrofuran provides the best results. Good yields of the phosphoranes are generally obtained when R^1 is an electron-withdrawing group such as ester or nitrile. The yields of phosphoranes obtained for the thiomethyl or phenyl cases can be

improved by using 1,4-diazabicyclo[2.2.2]octane (DABCO) rather than triethylamine as the base.

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TABLE I
PREPARATION OF (α -ACYLMETHYLENE)PHOSPHORANES FROM
 α -SUBSTITUTED METHYLPHOSPHONIUM SALTS²



R ¹	R ²	Solvent	Base	Yield (%)
CO ₂ Et	CF ₃	CH ₂ Cl ₂	Et ₃ N	54
CO ₂ Me	CF ₃	THF	Et ₃ N	99
CO ₂ Et	CF ₂ CF ₃	THF	Et ₃ N	69
CN	CF ₃	THF	Et ₃ N	75
SCH ₃	CF ₃	THF	Et ₃ N	49
Ph	CF ₃	CH ₂ Cl ₂	Et ₃ N	24
Ph	CF ₃	CH ₂ Cl ₂	DABCO	57

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 4,4,4-trifluorotetrolate: 2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester (10); (79424-03-6)

Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate: Butanoic acid, 4,4,4-trifluoro-3-oxo-2-(triphenylphosphoranylidene)-, ethyl ester (11); (83961-56-2)

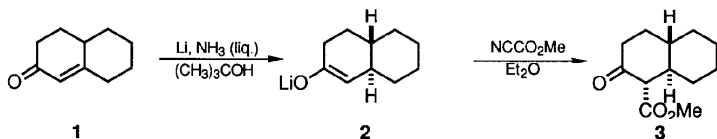
(Carbethoxymethyl)triphenylphosphonium bromide: Phosphonium, (carboxymethyl)triphenyl-, bromide, ethyl ester (8); Phosphonium, (2-ethoxy-2-oxoethyl)triphenyl-, bromide (9); (1530-45-6)

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride (8,9); (407-25-0)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Ethyl bromoacetate: Acetic acid, bromo-, ethyl ester (8,9); (105-36-2)

SYNTHESIS OF β -KETO ESTERS BY C-ACYLATION OF PREFORMED ENOLATES WITH METHYL CYANOFORMATE: PREPARATION OF METHYL (1 α ,4 α β ,8 α)-2-OXODECAHYDRO-1-NAPHTHOATE



Submitted by Simon R. Crabtree, Lewis N. Mander, and S. Paul Sethi.¹

Checked by Thierry Vandenheste and Leo A. Paquette.

1. Procedure

Caution! Cyanide salts are formed in this procedure. All procedures should be conducted in a well-ventilated hood and rubber gloves should be worn.

Liquid ammonia (350 mL) is dried over sodium amide for 20 min (Note 1), then distilled under a positive pressure of dry nitrogen into a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a dry ice condenser, rubber septum and magnetic stirring bar. The flask is cooled to -78°C and small pieces of lithium (1.11 g, 0.16 mol) (Note 2) are added over 10 min to afford a deep blue solution. A solution of enone **1** (10.08 g, 0.07 mol) (Note 3) in tert-butyl alcohol (5.10 g, 0.07 mol) (Note 4) and ether (40 mL) (Note 5) is added dropwise over a 15-min period at -78°C , and then sufficient isoprene (Note 6) is added dropwise to discharge the residual blue color of the reaction mixture. The ammonia is allowed to evaporate under a stream of dry nitrogen and the ether is removed under reduced pressure to leave a white foam. After a further 5 min under high vacuum, the nitrogen atmosphere is restored, the lithium

enolate **2** is suspended in dry ether (80 mL) at -78°C by vigorous stirring, and methyl cyanoformate (6.73 g, 0.08 mol) (Note 7) is added over a 5-min period. Stirring is maintained at this temperature for a further 40 min and then the mixture is allowed to warm to 0°C . Water (500 mL) and ether (200 mL) are added and the mixture is stirred vigorously until the precipitate has dissolved. After separation of the organic layer, the aqueous phase is extracted with ether (2 x 300 mL), the combined extracts are washed with water (200 mL) and brine (200 mL) (Note 8), and then dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure furnishes a pale yellow oil which is dissolved in hexane (200 mL); the solution is kept in the freezer (-28°C) for approximately 1.5 hr, after which time very pale yellow crystals of the β -keto ester **3** are deposited. These are collected by filtration at low temperature and after concentration of the mother liquors, two further crops are collected. Flash chromatography (ethyl acetate/hexane, 13:87) on silica gel (140 g) (Note 9) of the residue (3.5 g) from the remaining mother liquor followed by two recrystallizations affords further **3**. The total quantity of **3** obtained is 11.5-11.8 g (81-84% yield) (Note 10).

2. Notes

1. Sodium amide is generated in situ from sodium metal and a crystal of ferric nitrate. Sodium metal by itself is not an effective drying agent.
2. Lithium wire was purchased from Merck Schuchardt.
3. Enone **1** was prepared according to the procedure of Augustine, R. L.; Caputo, J. A. *Org. Synth., Coll. Vol. V* **1973**, 869.
4. tert-Butyl alcohol was purchased from Ajax Chemicals and was freshly distilled from calcium hydride.

5. Diethyl ether was purchased from Ajax Chemicals and was freshly distilled from sodium and benzophenone.

6. Isoprene was purchased from Eastman Kodak, Ltd.

7. Methyl cyanoformate was purchased from the Aldrich Chemical Company, Inc. The ethyl and benzyl analogues are also available. Small quantities up to 30 g are conveniently prepared by the method of Childs and Weber,² but several workers have found it to be unsatisfactory on a larger scale because of the generation of inseparable impurities.

8. The aqueous washings contain toxic lithium cyanide and should be treated with a strong oxidizing agent (e.g., potassium permanganate) before disposal.

9. Merck Kieselgel 60 silica gel was used.

10. A sample recrystallized twice from hexane had mp 48-49°C (Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.63%; Found C, 68.59; H, 8.93). The spectroscopic properties of this product are as follows: IR ($CHCl_3$) cm^{-1} : 3026, 2931, 2859, 1744, 1710, 1454, 1447, 1437, 1364, 1348, 1340, 1155, 1112; 1H NMR ($CDCl_3$) δ : 1.00-1.50 (m, 6 H), 1.65-1.8 (m, 5 H), 1.9-2.0 (m, 1 H CH), 2.30-2.50 (m, 2 H, CH_2), 3.12 (d, 1 H, J = 12), 3.76 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$) δ : 25.4, 25.9, 32.6, 32.9, 33.3, 40.5, 41.4, 45.5, 51.8, 53.8, 170.2, 205.6; Mass spectrum (m/z): 210 (M^+ , 34.6%), 192 (72), 122 (66), 108 (59), 95 (68), 94 (94), 81 (100), 79 (53), 67 (77), 51 (61).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

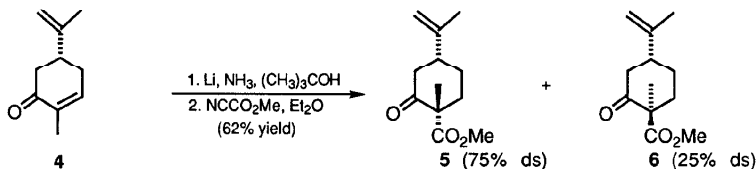
3. Discussion

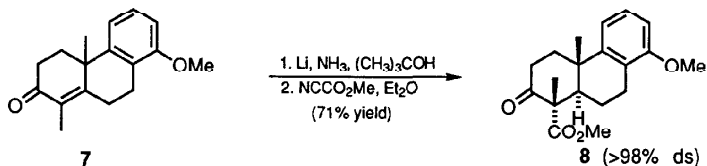
The present procedure provides an example of the regiospecific synthesis of β -keto esters by the C-acylation of preformed lithium enolates with cyanoformate esters.³ The enolates can be generated in a variety of ways, including direct enolization of ketones with suitable bases, liberation from silyl enol ethers and acetates, conjugate additions of cuprates to α,β -unsaturated enones and by the reduction of enones by lithium in liquid ammonia, as in the example described above. The more traditional acylating agents (acyl halides and anhydrides) afford variable amounts of O-acylated products⁴ and although the use of reaction temperatures of -100°C is reported to obviate this problem with some substrates,⁵ the method does not appear to be general. The classical solution has been to use carbon dioxide followed by esterification,⁶ but yields rarely exceed 50%, indicating, *inter alia*, that the formation of enol carbonates probably occurs to a significant extent and that these unstable intermediates decompose to ketones on work up.⁷ There is also the problem of handling thermally unstable β -keto acids. Carbon disulfide⁸ and carbon oxysulfide⁹ have been used instead of carbon dioxide, and the products methylated in situ to form dithio and thio esters, respectively. These can subsequently be converted into methyl esters by mercury(II) diacetate-catalyzed transesterification in methanol, but the methods are elaborate and do not appear to have found general use. Diethyl dicarbonate and its analogues show promise as possible alternatives to cyanoformates, but the reported yields to date are inferior.¹⁰

In the early investigations of this reaction it was found that in one comparative study of lithium, sodium and potassium enolates, only the lithium derivatives reacted satisfactorily,³ although sodium enolates have subsequently been used successfully.¹¹ A range of cyanoformates can be employed, but the tert-butyl derivatives have been reported to be too unreactive. However, a satisfactory

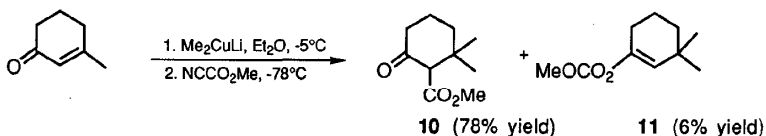
substitute which affords esters that can be de-alkylated with comparable facility is the *p*-methoxybenzyl analogue,¹² although it is prepared with some difficulty. In general, benzyl derivatives seem to give slightly better yields, possibly due to the more efficient isolation of products from substrates with lower molecular weights. Optically active cyanofomates derived from (+)-menthol, (-)-borneol, and the Oppolzer alcohol were reported to furnish good chemical yields, but the level of stereoselectivity was disappointingly low.¹³

For more conformationally-constrained chiral substrates, however, diastereoselectivity can be expected to be good to excellent. Lithium enolates derived from sterically unencumbered cyclohexanones undergo preferential axial acylation as illustrated by the reductive acylation of (*R*)-(-)-carvone **4** to afford a 3:1 mixture of esters **5** and **6**, whereas equatorial acylation is favored in compounds that possess an alkyl substituent in a 1,3-syn-axial relationship to the reacting center, as in the conversion of tricyclic enone **7** to ester **8** (epimeric with the product from the more traditional sequence of acylation followed by alkylation).¹⁴ (In substrates of this kind it is assumed that the transition state structure is based on a twist-boat conformation which permits the reagent to approach along an axial-like trajectory on the less encumbered, lower face of the substrate.)¹⁵





For compounds in which the β -carbon of the enolate is sterically hindered, this problem can normally be eliminated by the use of diethyl ether as the solvent. In several cases a switch from exclusive O-acylation in tetrahydrofuran to complete C-acylation in ether has been observed, and the conversion of **7** into **8** provides a typical illustration. When 3-methyl-2-cyclohexen-1-one **9** is converted into **10** by the addition of lithium dimethyl cuprate followed by in situ reaction with methyl cyanoformate, however, enol carbonate **11** accounts for 6% of the products. This can be avoided if the intermediate enolate is trapped as the enol trimethylsilyl ether and the enolate reliberated by treatment with butyllithium (note that the traditional reagent, methyllithium, is ineffective in ether as a solvent), but the overall yield is reduced.



Quite apart from the issue of regioselectivity, the present method is exceptionally reliable and makes it possible to prepare β -keto esters from ketones under especially mild conditions. It is not only the method of choice with sensitive substrates, but will often ensure superior results with more stable intermediates as well.^{8,16} A wide range of examples is provided in the Table, while further examples have been reported elsewhere.¹⁷ The methodology has also been applied to

esters,¹² lactones,¹⁸ and the N-acylation of lactams.¹⁹ The formation of β -diketones by the treatment of lithium enolates with alkanoyl and aroyl nitriles has also been described.²⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl cyanoformate: Formic acid, cyano-, methyl ester (8); Carbonocyanidic acid, methyl ester (9); (17640-15-2)

$\Delta^{1(9)}$ -Octalone-2: 2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro- (8,9); (1196-55-0)

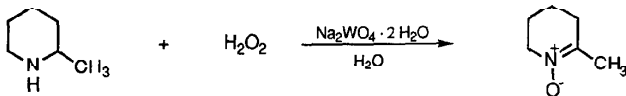
Isoprene (8); 1,3-Butadiene, 2-methyl- (9); (76-79-5)

TABLE
PREPARATION OF β -KETO-ESTERS BY THE KINETICALLY CONTROLLED
C-ACYLATION OF LITHIUM ENOLATES WITH METHYL CYANOFORMATE

Entry	Substrate	Procedure [†]	Product	Yield(%)
1		A		84 86
2		A		86 86
3		A		96
4		A		85
5		A		71 75
6		B		72 68
7		A		65
8		A		84
9		A		92
10		A		92
11		C		85

[†]Procedures: **A**: Reference 3; **B**: Lithium enolates generated by addition of methyllithium in THF at -78°C; **C**: As described for the conversion of enone 1 into β -

OXIDATION OF SECONDARY AMINES TO NITRONES
6-METHYL-2,3,4,5-TETRAHYDOPYRIDINE N-OXIDE
(Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide)



Submitted by Shun-Ichi Murahashi, Tatsuki Shiota, and Yasushi Imada.¹

Checked by Gary C. Look and Larry E. Overman.

1. Procedure

In a 500-mL, three-necked, round-bottomed flask equipped with a 100-mL pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar is placed 2.64 g (8.00 mmol) of sodium tungstate dihydrate (Note 1). After the flask is flushed with nitrogen, 40 mL of water and 23.5 mL (200 mmol) of 2-methylpiperidine (Note 2) are added. The flask is cooled with an ice-salt bath to -5°C (internal temperature) and 45.0 mL (440 mmol) of 30% aqueous hydrogen peroxide solution (Note 3) is added dropwise over a period of ca. 30 min. During the period of addition the reaction mixture should be carefully kept at a temperature below 20°C (Note 4). The cooling bath is removed, and the mixture is stirred for 3 hr (Note 5). Excess hydrogen peroxide is decomposed by adding ca. 3 g of sodium hydrogen sulfite with ice cooling (Note 6). The solution is saturated by adding ca. 25 g of sodium chloride and extracted with ten 200-mL portions of dichloromethane (Note 7). Combined organic extracts are dried over anhydrous sodium sulfate. The drying agent is removed by filtration, and the solvent is removed by a rotary evaporator keeping the

temperature at 40°C (Note 8) to give a pale yellow oil (20.0-22.0 g), which may be sufficiently pure for some applications (Note 9). Purification of the nitron is achieved by column chromatography on 300 g of silica gel packed in 97:3 chloroform/methanol in a 4.8-cm x 70-cm column (Note 10). The product is applied to the column in 10 mL of chloroform and the column is eluted with 97:3 chloroform/methanol. After twenty 100-mL fractions are collected, the eluent is changed to 8:2 chloroform/methanol, and another ten 100-mL fractions are collected and analyzed by thin layer chromatography (Note 11). Combination of fractions 16-30 and evaporation provides 14.0-15.7 g (62-70%) of pure 6-methyl-2,3,4,5-tetrahydropyridine N-oxide as a pale yellow oil (Notes 12 and 13).

2. Notes

1. Sodium tungstate dihydrate was purchased from Wako Pure Chemical Ind., Ltd. and used without further purification. The checkers employed material purchased from Mallinckrodt, Inc.

2. 2-Methylpiperidine purchased from Nacalai Tesque, Inc. was distilled prior to use (bp 119-120°C). The checkers employed 2-methylpiperidine purchased from Aldrich Chemical Company, Inc.

3. The 30% aqueous solution of hydrogen peroxide was purchased from Mitsubishi Gas Chemical Company, Inc. or Fisher Scientific. Ten percent excess of hydrogen peroxide is used to complete the reaction within an appropriate time.

4. This is an exothermic reaction. Higher reaction temperatures cause partial decomposition of the product.

5. The reaction mixture consists of the desired nitron and 6-15% of isomeric 2-methyl-2,3,4,5-tetrahydropyridine N-oxide: ^1H NMR (CDCl_3 , 500 MHz) δ : 1.53 (d, 3 H, $J = 6.9$, $-\text{CH}_3$), 7.14 (t, 1 H, $J = 3.9$, $-\text{CH}=\text{N}-$).

6. The presence of hydrogen peroxide is detected with potassium iodide-starch test paper.

7. Extraction with five 200-mL portions of dichloromethane gives 20-21 g of the product. Oxidation of secondary amines which have low molecular weights requires water as solvent. The nitrones thus obtained are highly soluble in water, and many extractions are required. However, other nitrones can be isolated easily by simple extraction.

8. Higher temperatures cause decomposition of the desired product, and lower temperatures retard the decomposition of the undesired nitron to give the dimeric compound.

9. The crude nitron consists of the desired nitron (85-70%), the 1:1 adduct of the less substituted nitron with the desired nitron [(3,14-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane) (15-30%), $R_f = 0.39$ (TLC glass plate silica gel 60 F₂₅₄, obtained from E. Merck, 9:1 chloroform/methanol); $m/e = 226.1681$ (C₁₂H₂₂N₂O₂), and the dimer of the desired nitron [(3,10-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane) (< 1%), mp 87.5-88.0°C; $R_f = 0.46$ (under the same conditions); $m/e = 226.1664$. The checkers found that the crude product decomposed noticeably when stored overnight at -20°C.

10. Silica gel 60 (70-230 mesh) was purchased from E. Morok. The checkers employed flash chromatography using a 20-cm x 7-cm column and 230-400 mesh EM silica gel 60. With this silica gel it is essential to have 1% triethylamine in the eluent.

11. The R_f value of the nitron is 0.37 (under the same conditions described above).

12. The product has the following spectral characteristics: IR (neat) cm⁻¹: 2945, 1627, 1448, 1190, 1165, 951, 872, 750, a strong OH stretch at 3400 cm⁻¹ is also apparent; ¹H NMR (CDCl₃, 500 MHz) δ : 1.71-1.77 (m, 2 H, H-4), 1.92-1.97 (m, 2 H, H-3), 2.11 (overlapping tt, 3 H, J = 1.5, 1.0, CH₃), 2.42-2.47 (m, 2 H, H-5), 3.78-3.83 (m, 2

H, H-2); ^{13}C NMR (CDCl_3 , 68 MHz) δ : 18.0 (CH_3), 18.2, 22.7, 30.0 (C-5), 57.3 (C-2), 145.1 (C-6); UV (EtOH) 235 nm (ϵ 6910).

13. The nitron slowly dimerizes at room temperature. It should be stored as a solution in a solvent such as dichloromethane to prevent dimerization.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Nitrones are highly versatile synthetic intermediates and excellent spin trapping reagents.² In particular, nitrones are excellent 1,3-dipoles³ and have been used for the synthesis of various nitrogen-containing biologically active compounds.^{3a,3b} The preparation of nitrones has been performed either by condensation of aldehydes or ketones with hydroxylamines,⁴ or by oxidation of the corresponding hydroxylamines.⁵ The difficulty of these methods is in the preparation of the starting hydroxylamines. For example, cyclic hydroxylamines are prepared from the corresponding cyclic amines via thermal decomposition of the corresponding tertiary amine N-oxides.⁶

The present procedure provides a single step synthesis of nitrones from secondary amines.⁷ Typical results of the preparation of nitrones are summarized in Table I. If necessary, the nitrones are easily purified by distillation, recrystallization, or column chromatography. Selenium dioxide is also an effective catalyst for the oxidation of secondary amines with hydrogen peroxide to give nitrones.⁸ 1,3-Dipolar

cycloadducts are obtained directly by the oxidation of secondary amines in the presence of alkenes.

The reaction of nitrones with various nucleophiles provides a powerful strategy for the introduction of a substituent at the α -position of secondary amines.⁹ The reaction of nitrones with Grignard reagents or organolithium compounds affords various α -substituted hydroxylamines, which can be converted into α -substituted secondary amines by catalytic hydrogenation. The nucleophilic reaction with potassium cyanide gives α -cyanohydroxylamines which are useful precursors for amino acids and N-hydroxyamino acids.¹⁰

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Appendix

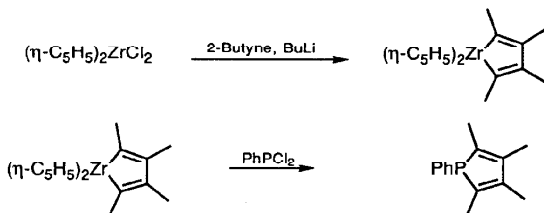
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 6-Methyl-2,3,4,5-tetrahydropyridine N-oxide: Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide (9); (55386-67-9)
- Sodium tungstate dihydrate: Tungstic acid, disodium salt, dihydrate (8,9); (10213-10-2)
- 2-Methylpiperidine: Piperidine, 2-methyl- (8,9); (109-05-7)
- Hydrogen peroxide (8,9); (7722-84-1)

TABLE
CATALYTIC OXIDATION OF SECONDARY AMINES
WITH HYDROGEN PEROXIDE

Amine	Solvent	Product	Yield (%)
	CH ₃ OH		89
	CH ₃ OH		74
	CH ₃ OH		85
	CH ₃ OH		85
	CH ₃ OH		86
	CH ₃ OH		60
	CH ₃ OH		62
	H ₂ O		44
	H ₂ O		40

1-PHENYL-2,3,4,5-TETRAMETHYLPHOSPHOLE
(1H-Phosphole, 2,3,4,5-tetramethyl-1-phenyl-)



Submitted by Paul J. Fagan and William A. Nugent.¹

Checked by Mark S. Jensen and James D. White.

1. Procedure

A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum-capped pressure-equalizing addition funnel on the center neck, rubber septum on one side neck, and a nitrogen inlet with stopcock on the other side neck is charged in a nitrogen-filled glove box (Note 1) with 27.0 g (92.5 mmol) of zirconocene dichloride [$(\eta\text{-C}_5\text{H}_5)_2\text{ZrCl}_2$] (Note 2). 150 mL of tetrahydrofuran (Note 3), and 16.0 mL (204 mmol) of 2-butyne (Note 4) added via syringe. The apparatus is removed from the glove box and attached via the nitrogen stopcock to a nitrogen bubbler. The flask is cooled to -78°C (dry ice-acetone bath) and 108 mL of 1.72 M butyllithium (186 mmol) in hexane (Note 5) is added via syringe to the addition funnel through the septum. The butyllithium solution is added dropwise to the stirred mixture in the flask. After the addition is complete, the reaction mixture is stirred at -78°C for 10 min (Note 6). The flask is allowed to warm by removing the dry ice-acetone bath, and

the reaction mixture is stirred at room temperature for 2.5 hr at which point the mixture is dark orange-red (Note 7). The flask is again cooled to -78°C , and 17.5 mL (129 mmol) of dichlorophenylphosphine (Note 8) is added in a slow stream via syringe through the septum on the flask. The dry ice-acetone bath is removed and the flask is allowed to warm to room temperature. After 1 hr the orange-red color has dissipated and the septa are replaced with glass stoppers. The nitrogen inlet is connected to a vacuum line (0.1 mm) and the solvent is removed under reduced pressure. The stopcock is closed and the apparatus is placed in a nitrogen-filled glove box (Note 1). The reaction residue is extracted three times with 30-mL portions of hexane, each of which is filtered from the precipitate of $(\eta\text{-C}_5\text{H}_5)_2\text{ZrCl}_2$ and combined. The hexane is removed under reduced pressure (0.5 mm), and the oily liquid that remains is transferred into a 100-mL round-bottomed flask. The flask is attached to a vacuum distillation apparatus with a 10-cm Vigreux column. The distillation apparatus is removed from the glove box and attached to a vacuum line. Distillation at 0.35 mm yields a fraction which is collected between $40\text{-}92^{\circ}\text{C}$ and discarded. A second fraction boiling between $92\text{-}104^{\circ}\text{C}$ (Note 9) is collected; the clear oily liquid is 1-phenyl-2,3,4,5-tetramethylphosphole [14.9-15.5 g, 75-78% based on $(\eta\text{-C}_5\text{H}_5)_2\text{ZrCl}_2$] (Note 10). The compound is air-sensitive and should be stored under nitrogen.

2. Notes

1. A nitrogen-filled glove bag may also be used.
2. Zirconocene dichloride was obtained from Aldrich Chemical Company, Inc. and used without further purification.
3. Tetrahydrofuran was distilled from sodium benzophenone ketyl before use.
4. 2-Butyne was obtained from Farchan Chemical Company and dried over 4 Å molecular sieves before use.

5. Butyllithium was obtained from Foote Mineral Co. The molarity was checked by titration of 2.00 mL of the butyllithium solution in 10 mL of diethyl ether with dry 2-butanol using 1,10-phenanthroline as indicator.

6. The reaction mixture may become thick with a white solid at this point. The solid can be loosened by manually shaking the flask, or with the aid of an external permanent magnet using the magnetic stirring bar to break up the solid. The solid loosens some more upon warming, and stirring is not a problem.

7. If desired, the zirconium metallacycle can be isolated at this point: The flask is attached to a vacuum line via the nitrogen inlet, and solvents are removed from the flask under reduced pressure. With the aid of a 40°C water bath, the reaction residue is thoroughly dried. The flask is sealed and placed in a nitrogen-filled glove box (Note 1). The residue is extracted with small portions of toluene (total of 50 mL), each portion being filtered and combined. Toluene is removed from the filtrate under reduced pressure. Hexane (20 mL) is added to the solid residue, and after trituration, the solid is collected by filtration, and washed once with 10 mL of hexane. It is dried under reduced pressure to yield 26.0 g (85%) of crystalline, orange-red (η -C₅H₅)₂ZrC₄(CH₃)₄ which is >95% pure by spectroscopic analysis. This compound is very stable thermally both in solution and in the solid state; however, it is air-sensitive and should be handled under nitrogen. It can be used as obtained as a reagent in the synthesis of other heterocycles. The NMR spectrum is as follows: ¹H NMR (300 MHz, THF-d₈) δ : 1.54 (s, 6 H, CH₃), 1.57 (s, 6 H, CH₃), 6.15 (s, 10 H, η -C₅H₅).

8. Dichlorophenylphosphine (Strem Chemicals, Inc.) was vacuum distilled and placed under a nitrogen atmosphere before use.

9. The boiling point has been reported previously as 105-110°C at 0.5 mm.²

10. The product has the following spectral properties: ¹H NMR (300 MHz, THF-d₈) δ : 1.89 (d, 6 H, J = 10.6, CH₃), 1.93 (s, 6 H, CH₃), 7.24 (m, 5 H, phenyl); ¹³C NMR (75.5 MHz, THF-d₈) δ : 12.9 (dq, J_{CH} = 126, J_{PC} = 22, CH₃), 13.9 (q, J_{CH} = 126, CH₃),

129.2 (dt, $J_{CH} = 160$ and 6, $J_{PC} = 8$, phenyl), 129.6 (dt, $J_{CH} = 162$ and 6, phenyl), 134.3 (ddt, $J_{CH} = 161$ and 5, $J_{PC} = 20$, phenyl), 134.7 (d, $J_{PC} = 15$), 136.4 (s, C=C), 143.4 (m, $J_{PC} = 11$); ^{31}P { 1H } NMR (121.7 MHz, THF- d_8) δ : 14 (s). Exact mass: Calcd. for $C_{14}H_{17}P$: $m/e = 216.1068$. Found: 216.1127.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Phosholes and other related heterocycles are an important class of main group compounds. The chemistry of phosholes and their preparation has been reviewed extensively by Mathay.³ We provide details here for a simple, one-pot procedure for the preparation of 1-phenyl-2,3,4,5-tetramethylphosphole applying zirconocene chemistry.⁴ The procedure involves reduction of $(\eta-C_5H_5)_2ZrCl_2$ with butyllithium in the presence of 2-butyne which (as reported initially by Negishi, et al.⁵) forms a zirconium metallacycle. Addition of dichlorophenylphosphine to this reaction mixture produces the phosphole. One other procedure for the preparation of 1-phenyl-2,3,4,5-tetramethylphosphole has been reported by Nief, et al.² That procedure involved aluminum chloride - coupling of 2-butyne, followed by reaction with dichlorophenylphosphine to form a chlorophospholium tetrachloroaluminate which was then reduced with tributylphosphine to produce the phosphole in 68% yield.

Using a procedure similar to that described here, or using isolated zirconium metallacycles as reagents, we have been able to prepare not only phospholes, but also arsoles, stiboles, bismoles, siloles, germoles, stannoles, galloles, thiophenes, selenophenes, and borole Diels-Alder dimers.⁴ Since a number of other titanium and zirconium metallacycles are readily available,⁴ these reagents should be useful in the preparation of a variety of heterocycles.

1. E. I. du Pont de Nemours and Co., Inc., Central Research and Development Department, Experimental Station, Box 80328, E328/364, Wilmington, DE 19880-0328. Contribution No. 5123. We thank Ronald J. Davis for technical assistance.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Phenyl-2,3,4,5-tetramethylphosphole: 1H-Phosphole, 2,3,4,5-tetramethyl-1-phenyl- (12); (112549-07-2)

Zirconocene dichloride: Zirconium, dichloro- π -cyclopentadienyl- (8); Zirconium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1291-32-3)

2-Butyne (8,9); (503-17-3)

Dichlorophenylphosphine: Phosphonous dichloride, phenyl- (8,9); (644-97-3)

Unchecked Procedures

Accepted for checking during the period June 1, 1990
through May 1, 1991. An asterisk (*) indicates that
the procedure has been subsequently checked.

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- 2551R* Tributyl (3-methyl-2-butenyl)tin.
Y. Naruta, Y. Nishigaichi, and K. Maruyama, Department of Chemistry, Faculty of Science, Kyoto University, Sakyo-ku, Kyoto 606, Japan
- 2552R* Ubiquinone-1.
Y. Naruta and K. Maruyama, Department of Chemistry, Faculty of Science, Kyoto University, Sakyo-ku, Kyoto 606, Japan
- 2571* 9-Bromo-9-phenylfluorene.
T. F. Jamison, W. D. Lubell, J. M. Dener, M. J. Krisché and H. Rapoport, Department of Chemistry, University of California, Berkeley, CA 94720
- 2576* Benzoannulation of Ketones.
M. A. Tius and G. S. K. Kannangara, Department of Chemistry, The University of Hawaii, Honolulu, Hawaii 96822
- 2577* 3-(1-Octen-1-yl)cyclopentanone.
R. C. Sun, M. Okabe, D. L. Coffen, and J. Schwartz, Chemistry Research Department, Hoffmann-La Roche Inc., Nutley, NJ 07110
- 2578 Asymmetric Hydrogenation of Allylic Alcohols Using BINAP-Ruthenium Complexes: (S)-(-)-Citronellol.
H. Takaya, T. Ohta, S.-i. Inoue, and R. Noyori, Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan
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M. Kitamura, N. Sayo, and R. Noyori, Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan
- 2581* Schwartz's Reagent.
S. L. Buchwald, S. J. LaMarie, R. B. Nielsen, B. T. Watson, and S. M. King, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139
- 2583* An Efficient Synthesis of Indole-2-acetic Acid Methyl Esters.
S. P. Modi, H. C. Oglesby, and S. Archer, Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180
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- 2588* Palladium(O)-Catalyzed Reaction of 9-Alkyl-9-borabicyclo[3.3.1]-nonane with 1-Bromo-1-phenylthioethene: 4-(3-Cyclohexenyl)-2-phenylthio-1-butene.
T. Ishiyama, N. Miyaura, and A. Suzuki, Department of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan
- 2589 (R)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2,c][1,3,2]oxazaborole.
L. C. Xavier and J. J. Mohan, Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, NJ 07065
- 2590* Preparation and Use of (Methoxymethoxy)-methylolithium: 1-(Hydroxymethyl)-cycloheptanol.
C. R. Johnson, J. R. Medich, R. L. Danheiser, K. R. Romines, H. Koyama, and S. K. Gee, Department of Chemistry, Wayne State University, Detroit, MI 48202
- 2591* A Hydroxymethyl Anion Equivalent: Tributyl-[(methoxymethoxy)methyl]stannane.
R. L. Danheiser, K. R. Romines, H. Koyama, S. K. Gee, C. R. Johnson, and J. R. Medich, Department of Chemistry, Wayne State University, Detroit, MI 48202
- 2592 Diastereoselective Homologation of (R)-2,3-O-Isopropylidene-glyceraldehyde Using 2-(Trimethylsilyl)thiazole: 2-O-Benzyl 3,4-isopropylidene-D-erythrose.
A. Dondoni, G. Fantin, and M. Fogagnolo, Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, 44100 Ferrara, Italy
- 2593R Spiroannulation of Enolsilanes: 2-Oxo-5-methoxyspiro[4.5]decane.
T. V. Lee and J. R. Porter, School of Chemistry, University of Bristol, Cantock's Close, Bristol, England BS8 1TS
- 2595* (R)-(+)-2-Hydroxy-1,2,2-triphenylethyl Acetate.
M. Braun, S. Schneider, and S. Houben, Institut für Organische und Makromolekulare Chemie, Heinrich-Heine Universität, Universitätsstrasse 1, D-4000 Düsseldorf, West Germany
- 2597 Benzocyclobutenone by Flash Vacuum Pyrolysis.
P. Schiess, P. V. Barve, F. E. Dussy, and A. Pfiffner, Institut für Organische Chemie, Universität Basel, St. Johannisring 19, CH-4056 Basel, Switzerland
- 2598* (1R,2R)-(+)- and (1S,2S)-(-)-1,2-Diphenyl-1,2-ethylenediamine.
S. Pikul and E. J. Corey, Department of Chemistry, Harvard University, Cambridge, MA 02138

- 2599R Enantioselective, Catalytic Diels-Alder Reaction: (1*S* endo) 3 (Bicyclo[2,2,1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone.
S. Pikul and E. J. Corey, Department of Chemistry, Harvard University, Cambridge, MA 02138
- 2602* Diethyl 1-Propyl-2-oxoethylphosphonate.
P. Savignac and C. Patois, Laboratoire de Chimie du Phosphore et des Métaux de Transition, DCPH, Ecole Polytechnique, 91128 Palaiseau Cedex, France
- 2603* Diastereoselective Formation of *trans*-1,2-Disubstituted Cyclohexanes from Alkylidenemalonates by an Intramolecular Ene Reaction: Dimethyl (1'*R*,2'*R*,5'*R*)-2-(2'-Isopropenyl-5'-methylcyclohex-1'-yl)-propane-1,3-dioate[4a].
L. F. Tietze and U. Beifuss, Institut für Organische Chemie der Universität Göttingen, Tammannstr. 2, D-3400 Göttingen, Federal Republic of Germany
- 2605* 2-Methylene-1,3-dithiolane.
K. R. Dahnke and L. A. Paquette, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2606R* Inverse Electron Demand Diels-Alder Cycloaddition of a Ketene Dithioacetal. Copper Hydride-Promoted Reduction of a Conjugated Enone. 9-Dithiolanobicyclo[3.2.2]non-en-2-one from Tropone.
K. R. Dahnke and L. A. Paquette, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2607* A Selective, Heterogeneous Oxidation Using a Mixture of Potassium Permanganate and Cupric Sulfate.
C. W. Jefford, Y. Li, and Y. Wang, Department of Organic Chemistry, University of Geneva, 1211 Geneva 4, Switzerland
- 2610* Ethyl 3-Oxo-4-pentenoate (Nazarov's Reagent).
R. Zibuck and J. Streiber, Department of Chemistry, Wayne State University, Detroit, MI 48202
- 2611* 3(*S*)-((*tert*-Butyldiphenylsilyl)oxy)-2-butanone.
L. E. Overman and G. M. Rishton, Department of Chemistry, University of California, Irvine, CA 92717
- 2612* Stereocontrolled Preparation of 3-Acyltetrahydrofurans from Acid-Promoted Rearrangements of Allylic Ketals: (2*S*,3*S*)-3-Acetyl-8-carboethoxy-2,3-dimethyl-1-oxa-8-azaspiro-[4.5]decane.
L. E. Overman and G. M. Rishton, Department of Chemistry, University of California, Irvine, CA 92717

CUMULATIVE AUTHOR INDEX

FOR VOLUME 70

This index comprises the names of contributors to Volume 70 only. For authors to previous volumes, see either indices in Collective Volumes I through VII or the single volume entitled *Organic Syntheses, Collective Volumes, I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

Arnold, H., 70, 111
Arnold, L. D., 70, 1, 10

Baum, J. S., 70, 93
Bigham, M. H., 70, 231
Bishop, R., 70, 120
Boger, D. L., 70, 79
Bonin, M., 70, 54
Bradshaw, J. S., 70, 129
Brown, D. S., 70, 157

Cantrell, Jr., W. R., 70, 93
Carrasco, M., 70, 29
Cava, M. P., 70, 151
Chen, H. G., 70, 195
Chen, W., 70, 151
Crabtree, S. R., 70, 256

Davies, H. M. L., 70, 93
Dickhaut, J., 70, 164

Fagan, P. J., 70, 272

Garner, P., 70, 18
Gibson, F. S., 70, 101
Giese, B., 70, 164
Gilheany, D. G., 70, 47
Grierson, D. S., 70, 54

Hamper, B. C., 70, 246
Helquist, P., 70, 177
Husson, H.-P., 70, 54
Huyer, G., 70, 1

Imada, Y., 70, 265

Jackson, Y. A., 70, 151
Johinson, M. R., 70, 68
Jones, R. J., 70, 29

Kamel, S., 70, 29
Kazlauskas, R. J., 70, 60
Kitamura, T., 70, 215
Knapp, S., 70, 101
Knochel, P., 70, 195
Krakowiak, K. E., 70, 129

Lenz, G. R., 70, 139
Lessor, R. A., 70, 139
Ley, S. V., 70, 157
Luh, T.-Y., 70, 240

Mander, L. N., 70, 256
Mattson, M. N., 70, 177
McDonald, F. E., 70, 204
McKee, B. H., 70, 47
Meister, P. G., 70, 226
Mozaffari, A., 70, 68
Murahashi, S.-I., 70, 265
Myles, D. C., 70, 231

Negron, A., 70, 169
Ni, Z.-J., 70, 240
Nugent, W. A., 70, 272

O'Connor, E. J., 70, 177
Overman, L. E., 70, 111

Panek, J. S., **70**, 79
 Pansare, S. V., **70**, 1, 10
 Paquette, L. A., **70**, 226
 Park, J. M., **70**, 18
 Patel, M., **70**, 79
 Pfau, M., **70**, 35

 Rapoport, H., **70**, 29
 Revial, G., **70**, 35
 Rumines, K. R., **70**, 93
 Royer, J., **70**, 54

 Sessler, J. L., **70**, 68
 Sethi, S. P., **70**, 256
 Sharp, M. J., **70**, 111
 Sharpless, K. B., **70**, 47
 Shiota, T., **70**, 265
 Sivik, M. R., **70**, 226
 Soderquist, J. A., **70**, 169
 Stang, P. J., **70**, 215
 Stephenson, E. K., **70**, 151

 Truong, T., **70**, 29

 Vederas, J. C., **70**, 1, 10

 Wender, P. A., **70**, 204
 White, A. W., **70**, 204
 Witschel, M. C., **70**, 111

 Yeh, M. C. P., **70**, 195

CUMULATIVE SUBJECT INDEX FOR VOLUME 70

This index comprises subject matter for Volume 70 only. For subjects in previous volumes, see the cumulative indices in Volume 69, which covers Volumes 65 through 69 and either the indices in Collective Volumes I through VII or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature. Both are usually accompanied by registry numbers in parentheses. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds appearing in the title of the preparation.

Acetamide, 2-(2-chloroethoxy)-N-ethyl-; (36961-73-6), **70**, 130
 Acetamide, N-[2-(2-hydroxyethoxy)ethyl]-; (118974-46-2), **70**, 130
 Acetamidoacrylic acid, **70**, 6
 p-Acetamidobenzenesulfonyl azide, **70**, 93
 p-Acetamidobenzenesulfonyl chloride, **70**, 93
 Acetic acid, bromo-, ethyl ester; (105-36-2), **70**, 248
 Acetic acid, diazo-, ethyl ester; (623-73-4), **70**, 80
 Acetic acid, isocyano-, ethyl ester; (2999-46-4), **70**, 70
 Acetic acid, lead (4+) salt; (546-67-8), **70**, 140
 Acetic acid, rhodium (2+) salt; (5503-41-3), **70**, 93
 Acetic acid, trifluoro-; (76-05-1), **70**, 141
 Acetic acid, trifluoro-, anhydride; (407-25-0), **70**, 246
 Acetic anhydride; (108-24-7), **70**, 69, 130
 Acetoacetic acid, 2-diazo-, ethyl ester, **70**, 94
 Acetoacetic acid, ethyl ester; (141-97-9), **70**, 94
 4-Acetoxy-3-nitrohexane, **70**, 69
 Acetylenes, perfluoroalkyl, **70**, 246
 α -ACETYLENIC ESTERS, **70**, 246
 O-Acetylserine, **70**, 6
 N-Acylaziridines, **70**, 106
 α -Acylmethylenephosphoranes, **70**, 251
 α -Alkylated piperidines, **70**, 57
 Alkylzinc iodide, **70**, 201
 ALKYNE-IMINIUM ION CYCLIZATIONS, **70**, 111
 Alkynyl(phenyl)iodonium sulfonates, **70**, 223
 ALKYNYL(PHENYL)IODONIUM TOSYLATES, **70**, 215
 ALLYLIC DITHIOACETALS, **70**, 240

Aluminum chloride; (7446-70-0), **70**, 226

Aluminum hydride reducing agents, **70**, 65

Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7), **70**, 20

Aluminum. hydrodiisobutyl-. **70**, 20

Aluminum trichloride, **70**, 162

α -Amino acids, **70**, 6

β -Amino alcohols, **70**, 58

2-(2-Aminoethoxy)ethanol, **70**, 129

Amino lactams, **70**, 106

α -Aminonitrile, **70**, 57

(S)-3-AMINO-2-OXETANONE P-TOLUENESULFONATE, **70**, 10

Ampurimycin studies, **70**, 27

Anhydrous acetonitrile, **70**, 2

Annulated lactams, **70**, 106

Arsoles, **70**, 276

Asymmetric dihydroxylation, **70**, 51

ASYMMETRIC SYNTHESIS OF SUBSTITUTED PIPERIDINES, **70**, 54

Azides, sulfonyl, **70**, 97

β -Azidoalanine, **70**, 15

Azido lactams, **70**, 106

Azobisisobutyronitrile, **70**, 151, 167

Barton-Zard pyrrole synthesis, **70**, 75

Benzazepine, **70**, 145

Benzazepinone, **70**, 144

2H-3-Benzazepin-2-one, 1,3,4,5-tetrahydro-7,8-dimethoxy-; (20925-64-8), **70**, 139

Benzene, (1-butyl-1-octen-3-ynyl)-, (E)-; (111525-79-2), **70**, 215

Benzene, 1,1'-(1,2-ethenediyl)bis-, (F)-; (103-30-0), **70**, 47
 Benzene, 1,1'-ethylidenebis-; (530-48-3), **70**, 179
 Benzene, ethynyl-; (536-74-3), **70**, 157
 Benzene, iodoso-, **70**, 217
 Benzenemethanamine, α -methyl-, (S)-; (2627-86-3), **70**, 35
 Benzenemethanamine, α -methyl-N-(2-methylcyclohexylidene)-; (76947-33-6), **70**, 35
 Benzenesulfonyl azide, 4-(acetylamino)-; (2158-14-7), **70**, 93
 Benzenesulfonyl chloride, 4-(acetylamino)-; (121-60-8), **70**, 93
 2-BENZENESULFONYL CYCLIC ETHERS, **70**, 15/
 Benzenethiol, copper(1+) salt; (1192-40-1), **70**, 206
 Benzylamine; (100-46-9), **70**, 112, 131
 Benzylamine, α -methyl-, (S)-(-)-, **70**, 35
 Benzyl chloroformate, **70**, 29
 4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXA-
 CYCLOHENEICOSANE (TRIAZA-21-CROWN-7), **70**, 129, 132
 N-Benzyl-4-hexyn-1-amine; (112069-91-7), **70**, 112
 (E)-1-BENZYL-3-(1-iodoethylidene)PIPERIDINE, **70**, 111
 N-(Benzyloxycarbonyl)-L-methionine methyl ester, **70**, 29
 N α -(BENZYLOXYCARBONYL)- β -(PYRAZOL-1-YL)-L-ALANINE, **70**, 2
 N-(BENZYLOXYCARBONYL)-L-SERINE, **70**, 1
 N-(Benzyloxycarbonyl)-L-serine β -lactone, **70**, 1
 N-(BENZYLOXYCARBONYL)-L-VINYLGLYCINE METHYL ESTER, **70**, 29
 9-Benzyl-3,9,15-triaza-6,12-dioxahaptadecane, **70**, 130
 Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (\pm);
 (5872-08-2), **70**, 112
 [1,1'-Binaphthalene]-2,2'-diol, (R)-(+)-; (18531-94-7), **70**, 60
 [1,1'-Binaphthalene]-2,2'-diol, (S)-(-)-; (18531-99-2), **70**, 60

(R)-(+)-1,1'-BI-2-NAPHTHOL, **70**, 60
 (S)-(-)-1,1'-BI-2-NAPHTHOL, **70**, 60
 (±)-1,1'-Bi-2-naphthyl pentanoate, **70**, 61
 (R)-1,1'-Bi-2-naphthyl pentanoate, **70**, 62
 Bismoles, **70**, 276
 1,2-Bis(2-iodoethoxy)ethane, **70**, 132
 Bis(trimethylsilyl)imidate, **70**, 104
 Bis(trimethylsilyl)methyl lithium, **70**, 243
 9-Borabicyclo[3.3.1]nonane; (280-64-8), **70**, 169
 9-BORABICYCLO[3.3.1]NONANE DIMER; (70658-61-6), **70**, 169
 9-Borabicyclo[3.3.1]nonane, 9-methoxy-; (38050-71-4), **70**, 173
 Boran-tetrahydrofuran, **70**, 131
 Borane, compd, with thiobis[methane] (1:1); (13292-87-0), **70**, 169
 Borane-methyl sulfide complex, **70**, 169
 Borate (1-), tetrafluoro-, sodium; (13755-29-8), **70**, 178
 Borole, Diels-Alder dimers, **70**, 276
 Boron trifluoride etherate, **70**, 22, 197, 217, 240
 Bovine pancreas acetone powder, **70**, 61
 1-Bromobutane; (109-65-9), **70**, 218
 Bromocresol green spray, **70**, 5, 13
 2-(3-Bromopropyl)-1H-isoindole-1,3(2H)-dione, **70**, 195
 2-Bromopyrrole, **70**, 155
 N-Bromosuccinimide, **70**, 155
 Butane, 1,4-dichloro-; (110-56-5), **70**, 206
 Butanoic acid, 2-diazo-3-oxo-, ethyl ester; (2009-97-4), **70**, 94
 Butanoic acid, 4,4,4-trifluoro-3-oxo-2-(triphenylphosphoranylidene)-,
 ethyl ester; (83961-56-2), **70**, 246

2-Butanol, (\pm)-; (15892-23-6), **70**, 206

2-Butanone, 4-[1-methyl-2-[(1-phenylethyl)imino]cyclohexyl]-, [S-(R*, S*)]-; (94089-44-8), **70**, 36

3-Butenoic acid, 2-amino-, hydrochloride, (S)-; (75266-38-5), **70**, 30

Butenoic acid, 4-(methylsulfinyl)-2-[[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)-; (75266-39-3), **70**, 30

3-Butenoic acid, 2-[[[(phenylmethoxy)carbonyl]amino]-, methyl ester, (S)-; (75266-40-9), **70**, 29

3-Buten-2-one; (78-94-4), **70**, 36

N-tert-BUTOXYCARBONYL-2-BROMOPYRROLE, **70**, 151

N-(tert-Butoxycarbonyl)-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline, **70**, 139

N-tert-Butoxycarbonylserine, **70**, 19

N-tert-Butoxycarbonyl-L-serine, **70**, 11

N-tert-BUTOXYCARBONYL-L-SERINE β -LACTONE, **70**, 10

N-tert-BUTOXYCARBONYL-2-TRIMETHYLSILYLPYRROLE, **70**, 151

N-tert-Butoxy-2,5-disubstituted pyrroles, **70**, 155

Butyllithium, **70**, 152, 154, 272

2-Butyne; (503-17-3), **70**, 272

2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester; (79424-03-6), **70**, 246

Calicheamycin fragment, **70**, 27

Camphorsulfonic acid monohydrate, **70**, 112

Carbamic acid, (2-oxo-3-oxetanyl)-, 1,1-dimethylethyl ester, (S)-; (98541-64-1), **70**, 10

5-Carbamoylpolyoxamic acid, **70**, 27

(Carbethoxymethyl)triphenylphosphonium bromide, **70**, 246

p-Carboxybenzenesulfonyl azide, **70**, 97

Celite filter, **70**, 122

3-Chloro-5,5-dimethylcyclohex-2-en-1-one, **70**, 205

N-[2-(2-Chloroethoxy)ethyl]acetamide, **70**, 130

Chloromethyl methyl sulfide, **70**, 177

Chloromethyltrimethylsilane, **70**, 241

Chlorotrimethylsilane; (75-77-4), **70**, 152, 164, 196, 216

Cholesterol esterase, **70**, 61

Cinchonan-9-ol, 10,11-dihydro-6'-methoxy-, 4-chlorobenzoate (ester),
(9S)-; (113162-02-0), **70**, 47

(E)-Cinnamaldehyde, **70**, 197, 240

Citric acid, **70**, 54

CONJUGATED ENYNES, **70**, 215

Copper(I) bromide-dimethyl sulfide complex, **70**, 218

Copper cyanide; (544-92-3), **70**, 196

Copper(I) thiophenoxide, **70**, 206

Copper-zinc organometallic, **70**, 196

Crown ethers, chiral, **70**, 65

2-CYANO-6-PHENYLOXAZOLOPIPERIDINE, **70**, 54

1,3-Cyclohexanedione, 5,5-dimethyl-; (126-81-8), **70**, 205

Cyclohexanone, 2-methyl; (583-60-8), **70**, 35

2-Cyclohexen-1-one, 3-chloro-5,5-dimethyl-; (17530-69-7), **70**, 205

Cyclohexylporphyrin, **70**, 77

1,5-Cyclooctadiene, (Z,Z)-; (1552-12-1), **70**, 120

1,5-Cyclooctadiene; (111-78-4), **70**, 169

Cyclopentadienyliron dicarbonyl dimer, **70**, 177

Cyclopentadienyliron dicarbonyl dimethylsulfonium tetrafluoroborate;
(72120-26-4), **70**, 179

1,3-Cyclopentanedione, 2-methyl-; (765-69-5), **70**, 226

Cyclopenta[b]pyrrol-2(1H)-one, hexahydro-6-iodo-, (3 α , 6 α , 6 α)-;
(100556-58-9), **70**, 101

2-Cyclopentene-1-acetamide; (72845-09-1). **70**, 101

2-Cyclopentene-1-acetic acid; (13668-61-6), **70**, 101

2-(2-Cyclopentenyl)acetyl chloride, **70**, 102

Cyclopropanation, **70**, 187

Cyclopropane, 1,1-diphenyl-; (3282-18-6), **70**, 177

Cyclopropenes, **70**, 97

DABCO, **70**, 253

Decahydroquinolines, **70**, 57

1,4-Diazabicyclo[2.2.2]octane, **70**, 253

1,8-Diazabicyclo[5.4.0]undec-7-ene, **70**, 70

Diazenedicarboxylic acid, diethyl ester; (1972-28-7), **70**, 10

Diazenedicarboxylic acid, dimethyl ester; (2446-84-6), **70**, 1

Diazomethane, **70**, 22

Diazo transfer reaction, **70**, 97

1,3-Dibromo-5,5-dimethylhydantoin, **70**, 151

1,2-Dibromoethane; (106-93-4), **70**, 196

Di-tert-butyl dicarbonate, **70**, 152

Di-tert-butyl pyrocarbonate, **70**, 140

Dicarboxylic acid, bis(1,1-dimethylethyl) ester; (24424-99-5), **70**, 18, 140, 152

Dichlorobis(triphenylphosphine)nickel, **70**, 241

1,4-Dichlorobutane, **70**, 206

Dichlorophenylphosphine, **70**, 273

(1 α , 2 α , 5 α , 6 α)-2,6-Dichloro-9-thiabicyclo[3.3.1]nonane, (10502-30-4), **70**, 120

2,6-Dicyanopiperidines, **70**, 55
 DIELS-ALDER REACTION OF AN HETEROCYCLIC AZADIENE, **70**, 79
 Diels-Alder reaction, inverse demand, **70**, 79
 Diels-Alder reactions, **70**, 85
 2-N,N'-Diethylaminomethyl-3,4-diethylpyrrole, **70**, 74
 Diethyl azodicarboxylate, **70**, 4, 10
 3,4-Diethyl-5-hydroxymethylpyrrole-2-carboxylic acid, **70**, 74
 3,4-DIETHYLPYRROLE, **70**, 68
 Dihalocarbene, **70**, 186
 3,4-Dihydro-6,7-dimethoxy-1-methylene, 1,1-dimethylethyl ester;
 (82044-08-4), **70**, 139
 Dihydroisoquinolines, **70**, 145
 1,4-DIHYDROPYRIDINE EQUIVALENT, **70**, 54
 Dihydroquinidine, benzoate ester, **70**, 49
 Dihydroquinidine 4-chlorobenzoate, **70**, 47
 Dihydroquinidine, 2-naphthoate ester, **70**, 49
 Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate, **70**, 80
 Diisobutylaluminum hydride, **70**, 20
 1,4- and 1,5-Dilithioalkanes, **70**, 211
 1,4-Dilithiobutane, **70**, 205
 Dimedone, **70**, 205
 Dimethoxyethane; (110-71-4), **70**, 169
 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline, **70**, 139
 2,2-Dimethoxypropane, **70**, 22
 7,8-DIMETHOXY-1,3,4,5-TETRAHYDRO-2H-3-BENZAZEPIN-2-ONE, **70**, 139
 Dimethyl azodicarboxylate, **70**, 1
 Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate, **70**, 80

N-[(1,1-Dimethylethoxy)carbonyl]-, methyl ester; (2766-43-0), **70**, 18
 N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester, **70**, 18
 1,1-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3-
 OXAZOLIDINECARBOXYLATE, **70**, 18
 3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidine-
 dicarboxylate, **70**, 19
 2,2-Dimethyl-3,4-oxazolidinedicarboxylate, **70**, 19
 Dimethyl 4-phenyl-1,2-diazine-3,6-dicarboxylate, **70**, 82
 Dimethyl 3-phenylpyrrole-2,5-dicarboxylate, **70**, 82
 9,9-DIMETHYLSPIRO[4.5]DECAN-7-ONE, **70**, 204
 Dimethyl sulfide; (75-18-3), **70**, 218
 Dimethyl sulfoxide; (67-68-5), **70**, 112, 122
 DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE, **70**, 79
 2,6-Dinitrato-9-thiabicyclo[3.3.1]nonane 9,9-dioxide, **70**, 125
 1,4-Dioxane; (123-91-1), **70**, 84, 179
 1,1-DIPHENYLCYCLOPROPANE, **70**, 177
 (R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL, **70**, 47
 (E)-1,2-Diphenylethene, **70**, 47
 1,1-Diphenylethylene, **70**, 179
 Disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate, **70**, 80
 cis-, trans-2,6-Disubstituted piperidines, **70**, 57
 2,6-Dithiaadamantane, **70**, 126
 1,3-Dithiolane, 2-styryl-; **70**, 240
 n-Dodecylbenzenesulfonyl azide, **70**, 97

 Enzyme mimics, **70**, 136
 Ethane, 1,2-bis(2-iodoethoxy)-; (36839-55-1), **70**, 132

1,2-Ethanediol: (540-63-6), **70**, 240
 1,2-Ethanediol, 1,2-diphenyl-, [R-(R*, R*)]-; (52340-78-0), **70**, 47
 Ethanol, 2-(2-aminoethoxy)-; (929-06-6), **70**, 129
 Ethyl acetoacetate, **70**, 94
 Ethyl bromoacetate, **70**, 248
 Ethyl diazoacetate, **70**, 80
 Ethyl diazoacetoacetate, **70**, 94
 Ethyl 5-(N,N'-diethylaminomethyl)-3,4-diethylpyrrole-2-carboxylate, **70**, 74
 Ethyl 3,4-diethylpyrrole-2-carboxylate, **70**, 70
 Ethylene, 1,1-diphenyl-, **70**, 179
 Ethyl formate, **70**, 232
 Ethylidene transfer reagent, **70**, 187
 Ethyl isocyanoacetate, **70**, 70
 ETHYL 2-METHYL-5-PHENYL-3-FURANCARBOXYLATE, **70**, 93
 ETHYL 4,4,4-TRIFLUOROTETROLATE, **70**, 246
 Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate, **70**, 246

 Ferric chloride, **70**, 180
 Flash chromatography, **70**, 4
 Formaldehyde; (50-00-0), **70**, 71, 112
 Formic acid, azodi-, diethyl ester, **70**, 10
 Formic acid, chloro-, benzyl ester; (501-53-1), **70**, 29
 Formic acid, chloro-, trichloromethyl ester; (503-38-8), **70**, 72
 Formic acid, cyano-, methyl ester, **70**, 256
 Formic acid, ethyl ester; (109-94-4), **70**, 232
 Formic acid, oxydi-, di-tert-butyl ester, **70**, 18, 140, 152
 Furan, **70**, 97

3-Furancarboxylic acid, 2-methyl-5-phenyl-, ethyl ester; (29113-64-2), **70**, 93

Furan, tetrahydro-, compd. with borane (1:1); (14044-65-6), **70**, 131

3-Furoic acid, 2-methyl-5-phenyl-, ethyl ester, **70**, 93

(-)-Galantic acid, **70**, 27

Galloles, **70**, 276

Germoles, **70**, 276

Glutaraldehyde, **70**, 54

Glycerol, **70**, 140

Glycine; (56-40-6), **70**, 30

Gooch tube, **70**, 226

Halo lactams, **70**, 106

Heterocyclic azadiene, **70**, 85

Heterodienophiles, **70**, 86

3-Hexanol, 3-nitro-; (5342-71-2), **70**, 68

3-Hexanol, 4-nitro-, acetate; (3750-83-2), **70**, 69

4-Hexyn-1-ol; (928-93-8), **70**, 111

4-Hexyn-1-ol, methanesulfonate; (68275-05-8), **70**, 111

4-Hexyn-1-yl methanesulfonate, **70**, 111

1-Hexyne; (693-02-7), **70**, 216

1-HEXYNYL(PHENYL)IODONIUM TOSYLATE, **70**, 215

Hydantoin, 1,3-dibromo-5,5-dimethyl-, **70**, 151

Hydrogen cyanide, **70**, 56

Hydrogen peroxide; (7722-84-1), **70**, 265

N-[2-(2-Hydroxyethoxy)ethyl]acetamide, **70**, 130

threo- β -Hydroxy-L-glutamic acid, **70**, 27

Hydroxy lactams. **70**. 106

1-Hydroxy-2-methylpent-1-en-3-one, **70**, 232

(E)-2-(4-HYDROXY-6-PHENYL-5-HEXENYL)-1H-ISOINDOLE-1,3(2H)-DIONE,
70. 195

2,4-Imidazolidinedione, 1,3-dibromo-5,5-dimethyl-; (77-48-5), **70**, 151

Imines, hydrolysis of. **70**. 36

Indolizidines, **70**, 57

8-exo-iodo-2-AZABICYCLO[3.3.0]OCTAN-3-ONE, **70**, 101

IODOLACTAMIZATION. **70**. 101

Iodomethane: Methane, iodo-; (74-88-4), **70**, 19, 113, 178

2-(3-Iodopropyl)-1H-isoindole-1,3(2H)-dione, **70**, 195

Iodosobenzene. **70**. 217

Iron, tetracarbonylbis (η^5 -2,4-cyclopentadien-1-yl)di-, (Fe-Fe); (38117-54-3), **70**, 177

1H-Isoindole-1,3(2H)-dione, 2-(3-bromopropyl)-; (5460-29-7), **70**, 195

1H-Isoindole-1,3(2H)-dione. 2-(4-hydroxy-6-phenyl-5-hexenyl)- :
(121883-31-6), **70**, 195

1H-Isoindole-1,3(2H)-dione, 2-(3-iodopropyl)-; (5457-29-4), **70**, 195

Isoprene; 1,3-Butadiene, 2-methyl-; (78-79-5), **70**. 256

Isopropylmagnesium chloride; (1068-55-9), **70**, 157

2(1H)-Isoquinolinecarboxylic acid, 3,4-dihydro-6,7-dimethoxy-1-methylene,
1,1-dimethylethyl ester: (82044-08-4)**70**.139

Isoquinoline, 3,4-dihydro-6,7-dimethoxy-1-methyl-; (4721-98-6), **70**, 139

ISOQUINOLINE ENAMIDES, **70**, 139

Ketene silyl acetals, **70**, 162

Keto carbenoids, **70**, 97

β -Ketoesters, C-acylation, **70**, 256

Kieselgel, **70**, 13

Kieselgel 60 silica gel, Merck, **70**, 258

β -Lactone, **70**, 1

Lead tetraacetate, for oxidative ring expansion of isoquinoline enamides, **70**, 139

Lewis acids catalysts, **70**, 65

Liquid ammonia, **70**, 256

2-Lithiofuran, **70**, 154

N-Lithiopyrrole, **70**, 154

2-Lithiothiophene, **70**, 154

Lithium; (7439-93-2), **70**, 205

Lithium aluminum hydride, **70**, 55

Lithium chloride; (7447-41-8), **70**, 196

Lithium, methyl-; (917-54-4), **70**, 165

Magnesium, chloro[(trimethylsilyl)methyl]-; (13170-43-9), **70**, 241

Methane, nitro-; (75-52-5), **70**, 183, 184, 226

Methanesulfonic acid, trifluoro-, trimethylsilyl ester; (27607-77-8), **70**, 101, 234

Methanesulfonyl azide, **70**, 97

Methanesulfonyl chloride; (124-63-0), **70**, 111

L-Methionine; (63-68-3), **70**, 31

L-Methionine, methyl ester, hydrochloride; (2491-18-1), **70**, 29

L-Methionine, (N-[(phenylmethoxy)carbonyl]-, methyl ester; (56762-93-7), **70**, 29

9-Methoxy-9-borabicyclo[3.3.1]nonane, **70**, 173

1-Methoxy-2-methylpenten-3-one, **70**, 237

(E,Z)-1-METHOXY-2-METHYL-3-(TRIMETHYLSILOXY)-1,3-PENTADIENE, **70**, 231

(S)-(-)- α -Methylbenzylamine, **70**, 35, 38

Methyl L-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate, **70**, 30

Methyl cyanoformate, **70**, 256

2-Methylcyclohexanone, **70**, 35

3-Methyl-2-cyclohexen-1-one, **70**, 261

2-METHYL-1,3-CYCLOPENTANEDIONE, **70**, 226

Methylene transfer reagent, **70**, 187

Methyl lithium-lithium bromide complex, **70**, 165

4-Methylmorpholine N-oxide, **70**, 47

(R)-(-)-10-METHYL-1-OCTAL-2-ONE, **70**, 35

(R)-(+)-2-Methyl-2-(3-oxobutyl)cyclohexanone; (91306-30-8), **70**, 36

METHYL (1 α ,4 α ,8 α)-2-OXODECAHYDRO-1-NAPHTHOATE, **70**, 256

Methyl 3-phenyl-5-carboxamidopyrrole-2-carboxylate, **70**, 85

2-Methylpiperidine, **70**, 265

6-METHYL 2,3,4,5-TETRAHYDOPYRIDINE N-OXIDE, **70**, 265

Methyl vinyl ketone, **70**, 35

Michael-type alkylation, **70**, 40

Mitsunobu conditions, **70**, 6

Molybdophosphoric acid, **70**, 31

Morpholine, 4-methyl-, 4-oxide; (7529-22-8), **70**, 47

Mosher ester, **70**, 24, 48

p-Naphthalenesulfonyl azide, **70**, 97

2(3H)-Naphthalenone. 4,4a,5,6,7,8-hexahydro-; (1196-55-0), **70**, 256

2(3H)-NAPHTHALENONE, 4,4a,5,6,7,8-HEXAHYDRO-4a-METHYL-,
(R)-; (63975-59-7), **70**, 35

Nickel-catalyzed coupling reactions, **70**, 243

Nickel, dichlorobis(triphenylphosphine)-; (14264-16-5), **70**, 241

1-Nitrocyclohexene, **70**, 77

4-Nitro-3-hexanol, **70**, 68

Nitromethane, **70**, 183, 184, 226

NITRONES, **70**, 265

1-Nitropropane, **70**, 69

Nitrosomethylurea, **70**, 22

2,3,7,8,12,13,17,18-OCTAETHYLPORPHYRIN, **70**, 68

Octahydrobinaphthol, **70**, 65

$\Delta^{1(9)}$ -Octalone-2, **70**, 256

ORGANOBIS(CUPRATES), **70**, 204

Osmium tetroxide; (20816-12-0), **70**, 47

Oxalyl chloride; (79-37-8), **70**, 101, 121, 205

Oxazolidine, **70**, 57

3,4-Oxazolidinedicarboxylic acid, 2,2-dimethyl-, 3-(1,1-dimethylethyl) 4-methyl ester, (S)-; (108149-60-6), **70**, 19

3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)- or (R)-; (S)- (102308-32-7); (R)- (95715-87-0), **70**, 18

5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-, [3R-(3 α ,5 β ,8 $\alpha\beta$)]-; (88056-92-2), **70**, 54

2-Oxetanone, 3-amino-, (S)-, 4-methylbenzenesulfonate; (112839-95-9), **70**, 10

OXIDATION OF SECONDARY AMINES, **70**, 265

Pentanedial; (111-30-8), **70**, 54

Pentanoic acid, [1,1'-binaphthalene]-2,2'-diyl ester, (\pm)-; (100465-51-8), **70**, 61

3-Pentanone; (96-22-0), **70**, 232

Pentanoyl chloride; (638-29-9), **70**, 61
 1-Penten-3-one, 1-hydroxy-2-methyl-; (50421-81-3), **70**, 232
 4-Pentyn-1-ol; (5390-04-5), **70**, 113
 Perfluoroalkyl acetylenes, **70**, 246
 1,10-Phenanthroline; (66-71-7), **70**, 206, 274
 Phenylacetylene; (536-74-3), **70**, 94, 157, 218
 (E)-5-PHENYLDODEC-5-EN-7-YNE, **70**, 215
 2-(2-Phenylethenyl)-1,3-dithiolane, **70**, 240
 (-)-Phenylglycine, **70**, 55
 (-)-Phenylglycinol; (56613-80-0), **70**, 54
 2-(Phenylsulfonyl)tetrahydro-2H-pyran, **70**, 157
 1-PHENYL-2,3,4,5-TETRAMETHYLPHOSPHOLE, **70**, 272
 1-Phenyl-1-(trimethylsiloxy)ethylene, **70**, 82
 Phosphine, triphenyl-; (603-35-0), **70**, 1, 248
 1H-Phosphole, 2,3,4,5-tetramethyl-1-phenyl-; (112549-07-2), **70**, 272
 Phosphomolybdic acid, **70**, 22
 Phosphonium, (carboxymethyl)triphenyl-, bromide, ethyl ester, **70**, 246
 Phosphonous dichloride, phenyl-; (644-97-3), **70**, 273
 Phthalimide, N-(3-bromopropyl)-, **70**, 195
 Piperidine, 2-methyl-; (109-05-7), **70**, 265
 Pirkle Type 1-A column, **70**, 64
 Polyaza-crown compounds, N-alkyl-substituted, **70**, 135
 Polyaza-crowns, **70**, 135, 136
 Poly(triphenylmethyl)methacrylate on silica gel (Chiralpak OT), **70**, 64
 Polyvalent iodine compounds, **70**, 222
 Porphine, 2,3,7,8,12,13,17,18-octaethyl-; (2683-82-1), **70**, 68
 Porphyrins, synthetic, **70**, 74

Potassium cyanide; (151-50-8), **70**, 55

Potassium iodide-starch test paper, **70**, 267

Potassium permanganate, **70**, 55

Propane, 1-nitro-; (108-03-2), **70**, 69

1,2,3-Propanetricarboxylic acid, 2-hydroxy-; (77-92-9), **70**, 54

1,2,3-Propanetriol; (56-81-5), **70**, 140

Propionaldehyde, **70**, 69

Propionitrile, 2,2'-azobis[2-methyl-; (78-67-1), **70**, 151

Propionyl chloride, **70**, 226

2H-Pyran, tetrahydro-2-(4-pentynyloxy)-; (62992-46-5), **70**, 113

2H-Pyran, tetrahydro-2-(phenylethynyl)-; (70141-82-1), **70**, 157

2H-Pyran, tetrahydro-2-(phenylsulfonyl)-; (96754-03-9), **70**, 157

Pyrazole, **70**, 1, 2

1H-Pyrazole; (288-13-1), **70**, 1

1H-Pyrazole-1-propanoic acid α -[[(phenylmethoxy)carbonyl]amino]-, **70**, 1

3,6-Pyridazinedicarboxylic acid, 4-phenyl-, dimethyl ester; (2166-27-0), **70**, 82

Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide; (55386-67-9), **70**, 265

Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro-; (6674-22-2), **70**, 70

Pyrrole; (109-97-7), **70**, 151

1H-Pyrrole-1-carboxylic acid, 2-bromo-, 1,1-dimethylethyl ester;
(117657-37-1), **70**, 151

1H-Pyrrole-2-carboxylic acid, 3,4-diethyl-, ethyl ester; (97336-41-9), **70**, 70

1H-Pyrrole-1-carboxylic acid, 2-(trimethylsilyl)-, 1,1-dimethylethyl ester;
(75400-57-6), **70**, 151

1H-Pyrrole-2,5-dicarboxylic acid, 3-phenyl-, dimethyl ester; (92144-12-2), **70**, 82

Pyrrole, 3,4-diethyl-; (16200-52-5), **70**, 68

Rhodium(II) acetate dimer, **70**, 93

Robinson-Schopf condensation, **70**, 56

Selenophenes, **70**, 276

Serine, **70**, 6

Serine, N-carboxy-, β -lactone, benzyl ester, L-; (26054-60-4), **70**, 1

Serine, N-carboxy-, N-tert-butyl ester, L-, **70**, 11, 19

L-Serine, N[(1,1-dimethylethoxy)carbonyl]-; (3262-72-4), **70**, 11, 19

L-Serine, N-[(phenylmethoxy)carbonyl]-; (1145-80-8), **70**, 1

Serine: L-Serine; (56-45-1), **70**, 18

Silane, (chloromethyl)trimethyl-; (2344-80-1), **70**, 241

Silane chlorotrimethyl-; (75-77-4), **70**, 152, 164, 216

Silane, 1-hexynyltrimethyl-; (3844-94-8), **70**, 215

Silane, [[1-(2-methoxy-1-methylethenyl)-1-propenyl]oxy]trimethyl-, (Z,E)-; (72486-93-2), **70**, 231

Silane, tetrachloro-; (10026-04-7), **70**, 164

Silane, trimethyl(4-phenyl-1,3-butadienyl)-, (E,E)-; (70960-88-2), **70**, 240

Silane, trimethyl[(1-phenylethenyl)oxy]-; (13735-81-4). **70**, 82

Silicon chloride, **70**, 164

Siloles, **70**, 276

Siloxy dienes, **70**, 237

Silyl enol ethers, **70**, 162

SILYLOLEFINATION, **70**, 240

Simmons-Smith reaction, **70**, 186

Sodium; (7440-23-5), **70**, 177

Sodium amide, **70**, 256

Sodium azide; (26628-22-8), **70**, 94

Sodium-benzophenone ketyl, **70**, 23
 Sodium hydride; (7646-69-7), **70**, 231
 Sodium iodide; (7681-82-5), **70**, 112, 195
 Sodium metabisulfite, **70**, 48
 Sodium periodate, **70**, 30
 Sodium taurocholate, **70**, 61
 Sodium tetrafluoroborate, **70**, 178
 Sodium tungstate dihydrate, **70**, 265
 D-erythro-Sphingosine, **70**, 27
 Spiroacetals, **70**, 160
 SPIROANNEALATION, **70**, 204
 Spiro[4.5]decan-7-one, 9,9-dimethyl-; (63858-64-0), **70**, 204
 Stannoles, **70**, 276
 STEREOSPECIFIC COUPLING WITH VINYL COPPER REAGENTS, **70**, 215
 Stilbene, (E)- **70**, 47
 Stiboles, **70**, 276
 2-Substituted dihydropyrans, **70**, 160
 2-Substituted tetrahydrofurans, **70**, 160
 Succinic acid, **70**, 226
 Sulfide, chloromethyl methyl; (2373-51-5), **70**, 177
 Sulfonyl azide, **70**, 93
 Sulfonyl chloride, **70**, 93
 Sulfur chloride; (10545-99-0), **70**, 121
 Swern oxidation, in presence of sulfur moiety, **70**, 126

 Tetrahydrobenzazepine, **70**, 145
 TETRAHYDRO-3-BENZAZEPIN-2-ONES, **70**, 139

Tetrahydro-2-(4-pentynyloxy)-2H-pyran, **70**, 113
 TETRAHYDRO-2-(PHENYLETHYNYL)-2H-PYRAN, **70**, 157
 Tetrahydropyranyl ethers, **70**, 160
 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, 1,2-dihydro-; (3787-09-5), **70**, 80
 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, 1,2-dihydro-, dimethyl ester;
 (3787-10-8), **70**, 80
 1,2,4,5-Tetrazine-3,6-dicarboxylic acid, 1,2-dihydro-, disodium salt;
 (96898-32-7), **70**, 80
 s-Tetrazine-3,6-dicarboxylic acid, dimethyl ester; (2166-14-5), **70**, 79
 2-Thiaadamantane, **70**, 126
 (endo,endo)-9-Thiabicyclo[3.3.1]nonane-2,6-diol, **70**, 121
 9-Thiabicyclo[3.3.1]nonane-2,6-diol, (endo,endo)-; (22333-35-3), **70**, 121
 9-THIABICYCLO[3.3.1]NONANE-2,6-DIONE; (37918-35-7), **70**, 120
 2-Thiabrexane, **70**, 126
 Thiacycloheptane, **70**, 126
 Thiacyclohexane, **70**, 126
 Thionyl chloride; (7719-09-7), **70**, 80, 130
 Thiophenes, **70**, 276
 Thymine polyoxin, **70**, 27
 p-Toluenesulfonic acid, **70**, 71
 p-Toluenesulfonic acid monohydrate; (6192-52-5), **70**, 13, 19, 217, 233
 Toluenesulfonyl azide, **70**, 97
 Transition metal carbene complexes, **70**, 186
 Triaza-21-crown-7, **70**, 132
 Tributylstannane, **70**, 166
 Trichloromethyl chloroformate, **70**, 72
 Trifluoroacetic acid; (76-05-1), **70**, 11, 141

Trifluoroacetic anhydride, **70**, 246

(E,E)-TRIMETHYL(4-PHENYL-1,3-BUTADIENYL)SILANE, **70**, 240

1-Trimethylsilyl-1-hexyne, **70**, 215

(Trimethylsilyl)methylmagnesium chloride, **70**, 241

Trimethylsilyl trifluoromethanesulfonate, **70**, 101, 234

Triphenylphosphine, **70**, 1, 248

Triphenylphosphine: Phosphine, triphenyl-; (603-35-0), **70**, 10

Trisilane, 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)-; (1873-77-4), **70**, 164

TRIS(TRIMETHYLSILYL)SILANE, **70**, 164

Urea, N-methyl-N-nitroso-; (684-93-5), **70**, 22

L-Vinylglycine hydrochloride, **70**, 30

Zinc; (7440-66-6), **70**, 195

Zinc bromide; (7699-45-8), **70**, 55, 157

Zinc-copper couple, **70**, 186

Zinc dust, **70**, 85

Zirconium, dichloro- π -cyclopentadienyl-, **70**, 272

Zirconium metallacycle, **70**, 274

Zirconocene dichloride, **70**, 272